This annual report was designed and produced by:
The Sanofi-Synthélabo Corporate Communications and Finance Departments and the Harrison&Wolf Agency.

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The photographs which illustrate this document feature Sanofi-Synthélabo employees: we would like to thank them for their contribution.

395 030 844 R.C.S. Paris
Group Profile

2nd pharmaceutical group in France
7th pharmaceutical group in Europe
One of the world’s top 20 pharmaceutical groups

Four areas of specialization
Sanofi-Synthélabo has a core group of four therapeutic areas:
• Cardiovascular / thrombosis
• Central nervous system
• Internal medicine
• Oncology
This targeted specialization enables the group to be a significant player in each of these areas.

Global dimension
Sanofi-Synthélabo is present in over 100 countries.
In Europe, the group has subsidiaries in every country.
In the United States, the group operates via a subsidiary, an alliance, a joint venture and license agreements.
In Japan, its products are marketed via joint ventures and license agreements.

Innovative and successful research
Sanofi-Synthélabo's R&D organization, targeted on the group's four core therapeutic areas, uses state-of-the-art technologies.
Sanofi-Synthélabo has a portfolio of 48 compounds in development, of which 20 are in phase II or III of clinical investigation and 28 in phase I clinical or preclinical development.
Chairman’s message

1. Results for 2001 were once again excellent. What were the highlights of the year?

The year 2000 ended with very positive results. 2001 was fundamentally even better for Sanofi-Synthélabo. True, net profit attributable to the Group before exceptional items and goodwill amortization, which rose by 54% in 2000, rose by only 43% in 2001... but the contribution from operations (excluding the impact of currency fluctuations, merger synergies and the increase of our share in the profits of Lorex) to this growth was much higher in 2001, at 34 points, against 24 points in 2000.

This performance was achieved thanks to strong top-line growth. Consolidated sales were 15% higher on a comparable basis, and developed sales advanced by 21%.

Another highlight of 2001 was the continuing success of our R&D efforts. Clinical results have paved the way for new indications for Plavix® (clopidogrel) and Aprovel®/Avapro® (irbesartan), but the most exciting development is the launch in 2002 of Arixtra® (fondaparinux sodium), which is poised to become our fourth blockbuster.

2. Did the three blockbusters drive sales growth?

Yes, these drugs generated spectacular growth in developed sales during 2001. The antithrombotic Plavix®/Iscover® topped 2 billion euros, posting 55% growth on a comparable basis relative to 2000. Sales of the antihypertensive agent Aprovel®/Avapro®/Karvea® increased by 37% to 924 million euros.

And the hypnotic Stilnox®/Ambien®/Myslee® (zolpidem) achieved 29% growth to 1,215 million euros.

Nevertheless, we are not solely dependent on these three products for consolidated sales growth. Sales of our top 15 products advanced by 25% on a comparable basis, and the top 100 by 18%. These figures show that, while our product portfolio is becoming increasingly concentrated, we also have a very broad, sound base of drugs delivering growth, often because they are well suited to local therapeutic needs.

3. And geographically?

Our global market presence is undoubtedly one of our strengths. During 2001, we out-performed the market in all geographic regions.

Outside the United States – which we can talk about later – pressure from the authorities to curb healthcare spending was particularly strong in 2001, particularly in Europe. This makes the global performance of Sanofi-Synthélabo all the more satisfying. It has been achieved by bolstering our sales and marketing resources – up from 8,636 staff at the end of 2000 to 10,336 at the end of 2001 – but above all thanks to the dedication of our people.
4. What about Sanofi-Synthélabo’s position in the United States?

2001 saw further success for our development strategy in the U.S. The U.S. contribution to developed sales went up from 31% in 2000 to 36% in 2001, while the contribution to operating profit rose from 34% in 2000 to 41% in 2001. This shows that the U.S. is a major driver of earnings growth for the Group.

Sanofi-Synthélabo’s sales force, which comprised 1,155 medical sales representatives at the end of 2000, had reached 2,068 by the end of 2001. This doubling of the sales force will enable us to take over 100% of the promotion of Ambien®, ensure the launch of Arixtra®, and boost our efforts on Avapro® and Plavix®. Our own resources are supplemented by those of Bristol-McIyers Squibb in the co-promotion of Plavix® and Avapro® and by Organon for Arixtra®.

By mobilizing such powerful resources to promote our flagship drugs in the U.S. market, we are well positioned to further enhance our presence in the world’s largest market.

5. You have mentioned the success of your research efforts. What were the highlights of 2001?

Research is of course the cornerstone upon which the future of any pharmaceutical company rests. For some years, the successes of our research efforts have accelerated our growth, giving us highly positive prospects for the medium and long term.

2001 saw the completion of the PRIME clinical trial program, which demonstrated the positive effect of Aprovel®/Avapro® in renal protection for hypertensive diabetic patients. The CURE study demonstrated the very significant short-term and long-term benefits of Plavix® in patients with acute coronary syndrome. Both these compounds are the subject of major ongoing clinical trials with a view to expanding their clinical indications.

However, the biggest event of 2001 was the submission of the new drug application for Arixtra® in the prevention of deep vein thrombosis following orthopedic surgery. Because this compound is wholly synthetic, it offers very high purity and safety levels. It has proved highly effective and should, on completion of ongoing supplementary indication programs, become a new blockbuster for the Group.

Turning to the portfolio of compounds in development, there are two particularly encouraging events: the commencement of phase III clinical trials for dronedarone in the treatment of cardiac rhythm disorders, and of rimonabant in the treatment of obesity. Both have a very good safety profile in areas where there exists a real therapeutic need.

Finally, we have stepped up our efforts in the biotechnology field, complementing our in-house expertise and existing agreements by developing new collaborations with Cephalon and IDM in oncology.

6. What are the challenges facing Sanofi-Synthélabo?

The challenges we face are really those facing the industry as a whole.

There is much talk about the expiry of patents for many major drugs, and of generics. The aim of our industry must be to conduct research on innovative therapeutic agents and make them available to patients. Pharmaceutical companies can only fund the growing cost of research and development if they can be assured of patent protection over a certain period of time. It is important for a company to be able to build its future on a regular schedule of patented products. From this point of view, Sanofi-Synthélabo enjoys excellent visibility.

However, we have recently had to respond to the filing of Abbreviated New Drug Applications (ANDAs) in the U.S. by two companies challenging the patents for Plavix® listed in the Orange Book of the Food and Drug Administration. We consider our position to be very solid until 2011, and in close collaboration with our partner Bristol-McIyers Squibb we have taken the necessary steps to defend our rights.
The loss of competitiveness of the European industry relative to the U.S. industry is a major concern. Much of this is due to the growing differential between the prices of drugs in the two markets, but the free movement of goods within the European Union constitutes a serious additional handicap for the European industry. This is because the reimbursement prices set by member states are wholly incompatible with the free movement of drugs. This results in the rapid growth of parallel distribution networks, which erodes the margins of pharmaceutical companies as prices are dragged down, while profiting intermediaries who bear none of the costs inherent in the discovery and production of drugs. Unless prices are liberalized, this process will have to be subject to very strict regulation if the European pharmaceutical industry is to survive.

The claim that everyone has a right to healthcare and medicines is now a major factor in the global pharmaceutical environment. The issue is too vast for the pharmaceutical industry alone, and any solution will require co-ordinated action at international level.

From the industry's standpoint, it is essential that the concept of intellectual property rights be respected, otherwise research will become impossible. But in major disease areas, and in their respective fields of excellence, pharmaceutical companies must clearly initiate specific actions. In the case of Sanofi-Synthélabo, we are focusing on malaria, still a major cause of mortality in many countries. Such initiatives must concern not only research and manufacturing, but also distribution of medicines in places where the disease is endemic and training of healthcare workers. Of course, this type of action can only be carried out in close collaboration with the medical, pharmaceutical and healthcare authorities in the countries concerned, and with international bodies such as the World Health Organization.

7. What are the prospects for Sanofi-Synthélabo?

For 2002, barring major adverse events, we can anticipate further strong growth in sales and profits. Over the medium term, our confidence is built on developing new indications for our major drugs and extending them to new geographic markets, in addition to the launch of Arixtra® and the quality of our portfolio of compounds undergoing development. The strengthening of our resources in the U.S. should lead to strong growth in that country's contribution to our profits, but all markets will contribute to the Group's overall growth.

Although we have the financial resources needed to seize acquisition opportunities, we will not do so unless we are convinced that they can add genuine value for our shareholders.

With the support of our shareholders, we will continue to pursue our goal of building a competitive, world-class pharmaceutical group. Our shareholders can rest assured that all our people are wholeheartedly committed to achieving this goal.

Jean-François Dehecq
Chairman and Chief Executive Officer
Key figures

Developed sales
(in millions of euros)
in 2001: 8,746
+21% on a comparable basis
of which pharmaceutical products
in 2001: 8,596
+21% on a comparable basis

Consolidated sales
(in millions of euros)
1999 5,350
2000 5,963
2001 6,488
of which pharmaceutical products
1999 4,718
2000 5,532
2001 6,339

Consolidated sales
of the three blockbusters
(in millions of euros)
Plavix®
1999 199
2000 437
2001 705
Aprovel®/Avapro®
1999 295
2000 300
2001 423
Stilnox®/Ambien®/Myslee®
1999 395
2000 582
2001 786

Developed sales
of the three blockbusters
(in millions of euros)
Plavix®
1999 635
2000 1,279
2001 2,033
Aprovel®/Avapro®
1999 385
2000 665
2001 924
Stilnox®/Ambien®/Myslee®
1999 615
2000 920
2001 1,215

Consolidated sales of pharmaceutical products by geographic area
- Europe 59%
- United States 17%
- rest of the world 17%
- Japan 5%

Developed sales of pharmaceutical products by geographic area
- Europe 45%
- United States 36%
- rest of the world 14%
- Japan 7%

Sanofi-Synthélabo 2001 Annual report
Consolidated sales of pharmaceutical products by therapeutic area

- cardiovascular/thrombosis: 41%
- central nervous system: 29%
- internal medicine: 23%
- oncology: 3%
- other: 4%

Operating profit (in millions of euros)

1999: 971
2000: 1,577
2001: 2,106

Operating profit by geographic area (excluding unallocated costs)

- Europe: 45%
- rest of the world: 14%
- United States: 41%

Employees by geographic area

- France: 11,842
- Europe excluding France: 8,674
- United States: 3,221
- Japan: 75

Employees by activity

- sales force: 10,336
- research and development: 6,273
- production: 7,651

Net profit attributable to the group before exceptional items and goodwill amortization (in millions of euros)

1999: 625
2000: 961
2001: 1,376

Developed sales include sales consolidated by Sanofi-Synthélabo, plus sales generated under the agreements with Bristol-Myers Squibb on Plavix® and Aprovel®/Avapro® and with Pharmacia on Stilnox®/Ambien®.

Sales of pharmaceutical products comprise sales generated by the ethical, OTC and generics businesses.
Stock exchange information

Listing
Sanofi-Synthélabo shares have been listed on the Premier Marché of the Paris Bourse since May 25, 1999 (Sicovam code 12057). The shares are included in the following benchmark indices:
- the CAC 40 French pan-sector index
- the Dow Jones Euro Stoxx 50 European pan-sector index
- the Dow Jones Stoxx Pharma European sector index.

Share capital
Sanofi-Synthélabo had share capital of 1,464,010,168 euros as at December 31, 2001, split into 732,005,084 shares with a par value of 2 euros.
Since December 31, 2000, the share capital has been increased by the issuance of 563,338 shares as a result of the exercising of options to subscribe for shares.
As at December 31, 2001, 906,338 options to subscribe for shares were still outstanding.

Trends in the Sanofi-Synthélabo share price

Base 100 as at December 30, 1998
Figures for the period prior to May 25, 1999 correspond to the stock market price of Sanofi shares, adjusted to take account of the merger parity and the four-for-one stock split.
Share ownership as at December 31, 2001

<table>
<thead>
<tr>
<th>Shares</th>
<th>Voting rights</th>
</tr>
</thead>
<tbody>
<tr>
<td>quantity</td>
<td>%</td>
</tr>
<tr>
<td>TotalFinaElf</td>
<td>190,800,756</td>
</tr>
<tr>
<td>L’Oréal</td>
<td>143,041,202</td>
</tr>
<tr>
<td>Treasury shares</td>
<td>11,419,291</td>
</tr>
<tr>
<td>Employees</td>
<td>7,004,436</td>
</tr>
<tr>
<td>Public</td>
<td>379,739,399</td>
</tr>
<tr>
<td>Total</td>
<td>732,005,084</td>
</tr>
</tbody>
</table>

* Based on the total number of voting rights published following the general meeting of May 22, 2001, i.e. 1,093,320,462.

TotalFinaElf and L’Oréal have entered into a shareholders' pact for an initial term of six years commencing December 2, 1998.

Shareholder information at a glance

<table>
<thead>
<tr>
<th></th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of shares as at December 31</td>
<td>731,143,218</td>
<td>731,441,746</td>
<td>732,005,084</td>
</tr>
<tr>
<td>Share price (in euros)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- High</td>
<td>46.35*</td>
<td>71.00</td>
<td>86.50</td>
</tr>
<tr>
<td>- Low</td>
<td>34.72*</td>
<td>34.70</td>
<td>52.60</td>
</tr>
<tr>
<td>- Last</td>
<td>41.34</td>
<td>71.00</td>
<td>83.80</td>
</tr>
<tr>
<td>Market capitalization (in millions of euros)</td>
<td>30,225</td>
<td>51,932</td>
<td>61,342</td>
</tr>
<tr>
<td>Ranking in CAC 40 by capitalization</td>
<td>15</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td>Consolidated earnings per share (in euros)</td>
<td>0.85</td>
<td>1.31</td>
<td>1.88</td>
</tr>
<tr>
<td>Net dividend per share (in euros)</td>
<td>0.32</td>
<td>0.44</td>
<td>0.66**</td>
</tr>
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</table>

* Since May 25, 1999.
** To be proposed at the general meeting of May 22, 2002.

Financial information

- Investor Relations: (+33) 1 53 77 45 45
- Toll-free shareholder line: (+33) 800 07 58 76
- Internet: www.sanofi-synthelabo.com
Corporate governance

Board of Directors

René Barbier de la Serre, aged 61
- Appointed in May 1999 to serve until 2004
- Chairman and Chief Executive Officer of Continentale d’Entreprises
- Director of Crédit Lyonnais and Nord-Est
- Member of the Supervisory Board of Compagnie Financière Saint-Honoré and Pinault-Printemps-Redoute

Robert Castaigne, aged 55
- Appointed in February 2000 to serve until 2004
- Chief Financial Officer of TotalFinaElf SA
- Chairman and Chief Executive Officer of Total Chimie and Total Nucléaire
- Director of Atofina, Compagnie Générale de Géophysique, Elf Aquitaine and Pétofina (Belgium)

Pierre Castres Saint Martin, aged 66
- Appointed in May 1999 to serve until 2004
- Director of Fimalac and SEB
- Chairman of the Supervisory Board of group Marc de Lacharrière

Jean-François Dehecq, aged 62
- Appointed in May 1999 to serve until 2004
- Chairman and Chief Executive Officer of Sanofi-Synthélabo
- Director of Air France and Péchiney
- Chairman of EFPIA (European Federation of Pharmaceutical Industries and Associations)

Thierry Desmarest, aged 56
- Appointed in February 2000 to serve until 2004
- Chairman and Chief Executive Officer of TotalFinaElf SA and Elf Aquitaine
- Member of the Supervisory Board of AREVA and L’Air Liquide

Hervé Guérin, aged 60
- Appointed in May 1999 to serve until 2004

L’Oréal
- Appointed in May 1999 to serve until 2004
- Represented by Michel Somnolet, aged 62
- Vice President of L’Oréal in charge of General Management, Administration and Finance
- Director of L’Oréal

Lindsay Owen-Jones, aged 56
- Appointed in May 1999 to serve until 2004
- Chairman and Chief Executive Officer of L’Oréal
- Director of BNP Paribas, Gesparal and Lafarge
- Member of the Supervisory Board of L’Air Liquide

Bruno Weymuller, aged 53
- Appointed in May 1999 to serve until 2004
- Executive Vice President, Strategy and Risk Assessment of TotalFinaElf SA
- Director of Elf Antar France, Elf Aquitaine, Atofina, and Technip Coflexip

Observers

Régis Dufour
René Sautier

At December 31, 2001, individual members of the Board of Directors together held a total of 271,727 shares.

Attendance fees totaling 365,500 euros were allotted to Board members of Sanofi-Synthélabo in respect of the year ended December 31, 2001. A detailed list of sums paid in 2001 is given in the Management Report.
Committees and Directors' code

At meetings held on May 19, 1999 and February 21, 2000, the Board of Directors of Sanofi-Synthelabo set up specialist committees and drew up a code for directors. Members of the committees are chosen from among the members of the Board, and appointed by the Board.

Committees

Audit committee, comprising:
René Barbier de la Serre
Michel Somnolet
Bruno Weymuller

The committee's role is to examine:
- the annual and interim financial statements;
- control procedures;
- appropriateness of accounting policies;
- internal audit programs and assignments;
- the annual review of major litigation;
- any issue liable to have a material financial or accounting impact;
- proposed appointments of auditors.

The committee is entitled to make site visits and conduct interviews in furtherance of its role. It may request interviews with those involved in the preparation and control of the financial statements, including the auditors.

The committee met twice during 2001.

Compensation and appointments committee, comprising:
René Barbier de la Serre
Thierry Desmarest
Lindsay Owen-Jones

The committee's role is to:
- formulate recommendations and proposals concerning the compensation of corporate officers and the granting of stock options;
- examine the allocation of attendance fees between directors and, where appropriate, observers;
- assist the Board in selecting new directors;
- advise the Chairman on the selection of key senior managers and their compensation.

The committee met three times in 2001.

Scientific committee, comprising:
Pierre-Gilles de Gennes
Jean-François Dehecq

The committee's role is to:
- report to the Board on technological changes liable to have an impact on the Company’s activities;
- give its opinion on the orientations of the Company's R&D;
- provide input in solving any technical issue encountered by the Company.

The committee met once in 2001

Directors

The Directors' code defines the rights and obligations of the members of the Board of Directors, and the role of the committees. When directors attend and vote at Board meetings, they represent all the shareholders and must act in the Company’s corporate interests. Directors must make every effort to attend meetings of the Board and of any committees of which they are members. They must devote the necessary time to examining the matters submitted to them. Directors must inform the Board of any conflict of interest, including potential ones, and may not become involved in a personal capacity in undertakings that are in competition with the Company without first informing the Board and obtaining its authorization.
Management Committee

Jean-François Dehecq
Chairman and Chief Executive Officer

Gérard Le Fur
Executive Vice President
Scientific Affairs

Hanspeter Spek
Executive Vice President
International Operations

Christian Mulliez
Senior Vice President
Chief Financial Officer

Pierre Lepienne
Executive Vice President
Corporate Affairs

Marie-Hélène Laimay
Vice President
Internal Audit

Jean-Claude Leroy
Senior Vice President
Strategy, Business Development & Information Systems

Nicole Cranois
Senior Vice President
Corporate Communications

Jean-Pierre Kerjouan
General Counsel
Senior Vice President
Legal Affairs

Jean-Claude Armbruster
Senior Vice President
Human Resources

Gilles Lhemould
Senior Vice President
Industrial Affairs

Christian Lajoux
Senior Vice President
France
Compensation of Management Committee members and stock options

The compensation of the Chairman and Chief Executive Officer and other Management Committee members is set after analyzing the practices adopted by the leading French and European industrial companies and the opinion of the compensation and appointments committee. In addition to base compensation, Management Committee members receive variable compensation, which is determined by the actual performance and growth of the business areas for which the manager concerned has responsibility. Variable compensation may reach over half of the base compensation.

Stock options may be granted in addition to compensation.

The total compensation paid to the twelve Sanofi-Synthélabo Management Committee members during the 2001 financial year was 6.19 million euros, including 1.53 million euros for the Chairman.

As at December 31, 2001, Management Committee members between them held 1,535,900 stock options, including 445,000 held by the Chairman.

On May 10, 2001, the Board of Directors of Sanofi-Synthélabo granted 2,936,500 stock options in favor of 848 beneficiaries at a price of 64.5 euros per share. Of these, a total of 434,000 were granted to the twelve Management Committee members of Sanofi-Synthélabo, including 145,000 to the Chairman. Each option entitles the holder to purchase one share. The options are exercisable on or after May 11, 2005. (Cf. chart below)

A statement of the outstanding stock option plans, showing for each plan the date on which the options were granted, the total number granted, the date from which the options are exercisable, the expiry date of the options, the exercise price and the total number of options exercised as of December 31, 2001, is provided in note D.12.3 of the consolidated financial statements as included in this report.

As at December 31, 2001, 906,388 options to subscribe for shares were still outstanding, representing a potential increase of 12 million euros in shareholders’ equity.

As at the same date, 11,251,585 shares remained to be purchased by beneficiaries of options to purchase shares.

In 2001, 881,313 shares were subscribed for or purchased by beneficiaries of stock options, including 88,000 by the Chairman.

### Outstanding stock option plans

#### Options granted

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<tbody>
<tr>
<td>Total number of options granted</td>
<td>364,000</td>
<td>1,435,600</td>
<td>1,550,000</td>
<td>1,492,800</td>
<td>1,382,080</td>
<td>1,496,400</td>
<td>716,040</td>
<td>4,292,000</td>
<td>2,936,500</td>
<td>15,665,420</td>
</tr>
<tr>
<td>- of which members of the Management Committee</td>
<td>5,200</td>
<td>175,040</td>
<td>255,360</td>
<td>155,200</td>
<td>233,000</td>
<td>229,200</td>
<td>57,200</td>
<td>467,000</td>
<td>434,000</td>
<td>2,011,200</td>
</tr>
<tr>
<td>Mr Dehecq</td>
<td>-</td>
<td>79,200</td>
<td>44,000</td>
<td>44,000</td>
<td>60,000</td>
<td>80,000</td>
<td>-</td>
<td>160,000</td>
<td>145,000</td>
<td>612,200</td>
</tr>
<tr>
<td>Purchase/subscription price (en €)</td>
<td>6.36</td>
<td>5.86</td>
<td>7.18</td>
<td>8.56</td>
<td>19.73</td>
<td>28.38</td>
<td>38.08</td>
<td>43.25</td>
<td>64.5</td>
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#### Options exercised in 2001

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<tbody>
<tr>
<td>Number of options exercised in 2001</td>
<td>1,000</td>
<td>167,284</td>
<td>251,146</td>
<td>444,683</td>
<td>6,000</td>
<td>11,200</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>881,313</td>
</tr>
<tr>
<td>- of which members of the Management Committee</td>
<td>-</td>
<td>-</td>
<td>106,600</td>
<td>82,400</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>189,000</td>
</tr>
<tr>
<td>Mr Dehecq</td>
<td>-</td>
<td>-</td>
<td>44,000</td>
<td>44,000</td>
<td>-</td>
<td>-</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>88,000</td>
</tr>
<tr>
<td>Number of options outstanding</td>
<td>13,400</td>
<td>70,000</td>
<td>491,956</td>
<td>884,857</td>
<td>1,338,480</td>
<td>1,483,200</td>
<td>711,880</td>
<td>4,243,500</td>
<td>2,920,700</td>
<td>12,157,973</td>
</tr>
<tr>
<td>- of which members of the Management Committee</td>
<td>-</td>
<td>-</td>
<td>53,500</td>
<td>68,000</td>
<td>227,000</td>
<td>229,200</td>
<td>57,200</td>
<td>467,000</td>
<td>434,000</td>
<td>1,535,900</td>
</tr>
<tr>
<td>Mr Dehecq</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>60,000</td>
<td>80,000</td>
<td>-</td>
<td>160,000</td>
<td>145,000</td>
<td>445,000</td>
<td></td>
</tr>
</tbody>
</table>

(1) In 1994, 1995 and 1996, there were both plans involving options to purchase shares and options to subscribe for shares.
“Performance and innovation: our research and development”

Research has always been at the heart of our strategy. Our efforts are focused on the major public health challenges corresponding to our areas of expertise: cardiovascular/thrombosis, central nervous system, oncology and internal medicine.

An expenditure of more than 1 billion euros on research and development.

+6,000 scientific and support staff.

An international organization.
Marketing authorization submissions and approvals in 2001

In 2001, the major research efforts of Sanofi-Synthélabo in its four areas of expertise (cardiovascular/thrombosis, central nervous system, immuno-oncology and internal medicine) culminated in the granting of approvals or the submission of marketing authorization applications for several new chemical entities, as well as in extensions of the indications of recently marketed products.

Cardiovascular / thrombosis

Arixtra®
fondaparinux sodium
Marketing authorization applications were submitted in Europe and in the United States in February 2001. Approval was received in December 2001 in the U.S., after a priority review, and in March 2002 in Europe, for the indication “Prevention of venous thromboembolic events in patients who have undergone major orthopedic surgery of the lower limbs, such as hip fracture, or knee or hip replacement surgery”.

Plavix®
clopidogrel
An application for extension of the indication of Plavix® to “Acute coronary syndrome” was submitted in August 2001 in the United States, where it was granted a priority review, and in November 2001 in Europe. In February 2002, the U.S. health authorities approved this extension of the indication.

Aprovel® / Avapro®
irbesartan
An application for extension of the indication of Aprovel®/Avapro® to “Nephropathy induced by type 2 diabetes” was submitted in August 2001 in the United States, where it was granted a priority review, and also in Europe. In early 2002, the Advisory Committee on cardiovascular and renal products of the Food and Drug Administration (FDA) in the U.S. gave a split vote (five against six) on approval of this extension of the indication. Bristol-Meyers Squibb and Sanofi-Synthélabo subsequently withdrew the application for extension of the indication in order to have time to respond to the questions raised, prior to resubmitting the dossier.
In March 2002, the Committee for Proprietary Medicinal Products (CPMP) recommended granting marketing authorization in Europe for irbesartan in the treatment of diabetic renal disease.

Central nervous system

Xapril®
xaliproden
A marketing authorization application for the indication “Amyotrophic lateral sclerosis” was submitted in June 2001 in Europe.

Internal medicine

Xatral® once-daily
alfuzosine
In the United States, an Approvable Letter was received from the Food and Drug Administration (FDA) in October 2001 with respect to a marketing authorization for the indication “Symptomatic treatment of benign prostatic hyperplasia”.

Oncology

Fasturtec®
rasburicase
A marketing authorization for the indication “Treatment and prevention of chemotherapy-induced hyperuricemia in malignant diseases” was granted by the European Commission in February 2001. Registration is ongoing in the U.S.
Other development activities in 2001

Phase III studies were initiated in 2001 on two products from the research of Sanofi-Synthélabo:
- dronedarone (SR 33 589) in the secondary prevention of atrial fibrillation episodes;
- rimonabant (SR 141 716) in the treatment of obesity.

Multiple research strategies

Sanofi-Synthélabo has chosen to concentrate its research and development efforts on four therapeutic areas: cardiovascular/thrombosis, central nervous system, internal medicine and oncology. To identify compounds for proposal as development candidates, its teams employ various strategies differing widely in their nature and objectives.

Research and development portfolio

Sanofi-Synthélabo has a portfolio of 48 compounds under development, of which 20 are in phase II or in phase III of clinical investigation.

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Preclinical</th>
<th>Phase I</th>
<th>Phase IIa</th>
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As of January 31, 2002
A project-oriented organization

The objectives of speed, cost and quality have led to a project-oriented organization within the Development Division, continuing throughout compound development from the preclinical phase to the development of new indications for products already on the market.

This organization ensures consistency and continuity of development, optimizes the use of resources, and facilitates the transfer of expertise concerning all the activities in each department required for obtaining a marketing authorization.

Research agreements and technological approaches

Joint projects with biotechnological companies and other pharmaceutical firms have enabled the research teams of Sanofi-Synthélabo to gain access to new technologies and techniques and to expand or reinforce its current areas of research.

• In genomics:
  - Exploitation of the genomic database of Human Genome Sciences Inc. (Rockeville, U.S.) has enabled the identification of new biological targets which are currently being investigated for their potential value for in the discovery of new therapeutic agents.
  - The joint project with Genset (Paris, France) has permitted investigation of the existence of polymorphisms on 16 human genes relevant to central nervous system disorders.

• In functional genomics:
  - The joint project initiated in 1999 with Genfit (Lille, France) was reinforced in 2001. Through this agreement, it is planned to study inflammatory phenomena affecting the arterial wall likely to lead to the identification of new and original biological targets relevant to the treatment of atherosclerosis.
  - The joint project initiated in 2001 with Genoway (Lyon, France) provides access to specific expertise concerning the study of murine embryonic stem cells which should enable the development of screening tools by means of genetic modifications, either in cell culture or in whole organisms. This program forms part of a large co-operative project involving the French Ministry of Industry, INRA and INRIA.
  - The joint project with Lifespan (Seattle, U.S.), initiated in 2001, has provided access to a database permitting the location and validation of the function of 300 receptors coupled to G proteins already identified in the human genome.

  • In molecular screening:
    - The joint project with CEREP (Rueil-Malmaison, France), started in 1997, has been prolonged. In the context of this contract, it is planned to synthesize chemical libraries enriching the chemical resources of the group and to screen these libraries on new biological targets of interest. The discovery of new chemical leads active on the selected targets permitted the implementation of a chemical optimization program during 2001.

  • With regard to the search for new development candidates:
    - The research and development agreement concluded with Mitsubishi-Pharma Corp. (Tokyo, Japan) in 1998, with the objective of identifying new neuroprotective agents intended for the treatment of neurodegenerative disorders, has been renewed for a further two years.
    - A research and development agreement was concluded in December 2001 with Cephalon (West Chester, U.S.) giving access to a new compound inhibiting angiogenesis, CEP 7055, potentially a future anti-cancer agent, as well as to a research program designed to identify new compounds with a similar mechanism of action.
    - Furthermore, the joint project with Organon (Oss, Netherlands) in the area of antithrombotic oligosaccharides is continuing.
    - In January 2002, Sanofi-Synthélabo and IDM (Paris, France) signed an agreement on co-operation in cellular immunotherapy for the development and marketing of immunologic treatments in the cancer area.
Dronedarone is targeted in the first instance at the prevention of recurrence of the most frequent form of cardiac rhythm disorder: atrial fibrillation. External electric shock treatment is the usual therapy for acute atrial fibrillation. To prevent recurrences, which are extremely common, this is generally followed by treatment with an anti-arrhythmic agent. The reference antiarrhythmic is still amiodarone, marketed by Sanofi-Synthélabo since the late 1960s under the brand name Cordarone®. With dronedarone, a potential successor to Cordarone®, the aim of Sanofi-Synthélabo is to offer a new treatment which is at least equally effective and with an improved safety profile compared with amiodarone. The results of the phase IIb DAFNE study were satisfactory. Tested at three different doses, dronedarone showed good efficacy and an excellent safety profile. The median time to recurrence was 56.24 days at a dose of 400 mg twice daily, compared with 5.32 days with placebo. Dronedarone was also effective with regard to the secondary endpoints: spontaneous cardioversion (return to normal cardiac rhythm) and ventricular rhythm in the event of recurrence. Finally, the compound has a good safety profile and, in particular, has no effect on the thyroid and lungs. Phase III studies on this highly promising product started in 2001.

Amyotrophic lateral sclerosis is a rare neurological disorder caused by degeneration of the motor neurons responsible for muscular function. It induces progressive paralysis leading to invariably fatal respiratory failure. It may affect young adults. Xaliproden, a non-peptide compound, activates the synthesis of endogenous neurotrophins. It is orally active with once-daily dosing. Its efficacy as a curative or preventive treatment has been demonstrated in vitro and in vivo in numerous animal models of central or peripheral neurodegeneration. In humans, xaliproden succeeded in slowing the decline in functional performance in a phase IIa trial. Two phase III studies, including over 2,000 patients, were completed in 2000. One evaluated xaliproden used as a single agent, the other assessing its efficacy in combination with riluzole versus riluzole alone. Both trials demonstrated beneficial effects of xaliproden on respiratory function and the factors contributing to disease progression. A marketing authorization application was submitted in June 2001 in Europe, where xaliproden has been qualified as an orphan drug for the treatment of this serious disorder.
osanetant and eplivanserin
Schizophrenia
Phase II

Confronted with the challenge of simultaneously evaluating the therapeutic activity of four compounds with novel mechanisms of action in schizophrenia, Sanofi-Synthélabo designed an original study protocol, METATRIAL, permitting the assessment of four products in the same study versus placebo and a calibrator, haloperidol. Technically, this new protocol proved satisfactory, the calibrator showing a therapeutic activity statistically different from that of placebo. Furthermore, the low variability between the different treatments and the different centres permitted pooling of the results. Indirectly validating the study design, rimonabant (SR 141716, a CB1 receptor antagonist) and SR 48692 (a neurotensin receptor antagonist) proved to be devoid of therapeutic activity. In contrast, osanetant (SR 142801, an NK3 receptor antagonist) showed an activity and a profile close to those of haloperidol with very good safety. Eplivanserin (SR 46349, a 5-HT2A receptor antagonist) proved to be particularly active against the depressive syndromes of schizophrenia. The development program is being continued for these two latter compounds.

Internal medicine

rimonabant
Obesity
Phase III

Reducing obesity is a public health necessity. The majority of currently available treatments are anorexigenic, i.e. they reduce food intake. Another therapeutic alternative is to prevent lipid absorption.

Demonstration of the presence in the brain of receptors for the active substance of cannabis, tetrahydrocannabinol which stimulates appetite, as well as for anandamide, a comparable substance secreted by humans, opened up a new and original approach. Rimonabant exploits this mechanism of action. The only selective antagonist of cannabinoid CB1 receptors known at present, it principally reduces lipid and carbohydrate intake, thereby controlling obesity. A previous phase IIa trial confirmed its efficacy in obese patients, showing loss of weight and decreased lipid and carbohydrate consumption. In a phase IIb trial, rimonabant once again achieved a significant weight loss in obese patients while showing a very good safety profile. Phase III studies, including over 5,000 patients, started in 2001.

Oncology

tirapazamine
Non-small-cell lung cancer in combination with cisplatin and vinorelbine
Phase III

Tirapazamine is an anti-cancer agent that is not directly cytolytic, but promotes the destruction of resistant hypoxic cells. This innovative mechanism of action is likely to diminish the rate of relapse. Submission of a marketing authorization application for tirapazamine in non-small-cell lung cancer is scheduled at the end of 2003 in Europe and the United States. Clinical studies in other indications, such as ENT cancers (particularly laryngopharyngeal cancers) are ongoing.
Once again, the progression of Sanofi-Synthelabo’s sales outperformed market growth, powered by its blockbusters and its well-balanced product portfolio. The launch of the antithrombotic Arixtra®, the reacquisition of rights to Ambien® and the expanded therapeutic indications for Plavix® and Aprovel® will support growth in 2002.

+44% increase in consolidated sales of our three blockbusters.

+25% increase in consolidated sales of the top 15 drugs combined.
Our new products

The approval of Arixtra® was obtained in December 2001 in the U.S. and in March 2002 in Europe.

Arixtra®
fondaparinux sodium
Prevention of venous thromboembolic events after orthopedic surgery

Deep-vein thrombosis is triggered by three factors: coagulation factor abnormalities, vascular wall injuries and venous stasis, occurring notably during prolonged immobilization. The risk of thrombosis is particularly high after surgery. In the absence of treatment, thrombosis occurs in 40% to 50% of patients undergoing hip replacement and in 70% to 80% of those undergoing total knee replacement. Venous thrombosis may be manifested locally by pain or edema of the leg, but it may also have more dramatic consequences, such as potentially fatal pulmonary embolism.

The aim of current treatments, primarily low molecular weight heparins, is to prevent such thrombosis. These treatments achieve a two- to three-fold reduction in the frequency of thrombosis.

A novel compound co-developed by Sanofi-Synthélabo and Organon (Akzo Nobel), fondaparinux sodium is the first representative of a new class of antithrombotics: selective inhibitors of coagulation Factor Xa. Arixtra® blocks a key step in the coagulation cascade, thereby preventing the formation of blood clots.

A product of polysaccharide chemistry, Arixtra® is a totally synthetic compound, a characteristic conferring a high level of purity. For both these reasons, Arixtra® constitutes a real technological and therapeutic advance. Its development potential promises to be substantial.

The first clinical indication is the prevention of deep-vein thrombosis in patients at high risk of thromboembolism after orthopedic surgery of the lower limbs.

Phase III studies, including over 7,000 patients, have demonstrated a major clinical benefit compared with the reference low-molecular-weight heparin. In patients with hip fracture, the risk of deep-vein thrombosis, around 20% with the reference treatment, falls to 8% with Arixtra®. The safety profile of the two treatments is similar.

In February 2002, Arixtra® was launched in the U.S., where it was approved for the prevention of venous thromboembolic events after orthopedic surgery in December 2001, following a priority review.

In Europe, Arixtra® was approved in the same indication in March 2002.

In Japan, the product is in phase IIb/III.
Sanofi-Synthélabo is initiating a program of extension of the indications of Arixtra® that will cover all segments of the market:
- Treatment of venous thrombosis: phase III trials (the MATISSE studies) are ongoing in 4,400 patients with the aim of submitting a marketing authorization application at the end of 2002 or in early 2003;
- The benefit of prolonged prophylaxis lasting 30 days versus short-term prophylaxis lasting five to nine days;
- The prevention of venous thrombosis in other types of surgery, such as abdominal surgery;
- The prevention of venous thrombosis in medical patients at high risk of venous thromboembolic events who have not undergone surgery;
- Acute coronary syndromes (unstable angina, coronary angioplasty, myocardial infarction): the initial efficacy results were confirmed by the phase IIb study PENTUA; these results, presented at the Scientific Sessions of the American Heart Association in November 2001, forecast a good benefit/risk ratio compared to current therapies. Arixtra® will be marketed by Sanofi-Synthélabo and Organon in the U.S., Canada and Mexico, and marketed by Sanofi-Synthélabo alone in Europe and in the rest of the world (excluding Japan).

**Fasturtec®**
rasburicase
Treatment and prevention of chemotherapy-induced hyperuricemia in malignant disease

An abrupt rise in blood uric acid levels, or hyperuricemia, is very common and pronounced in the context of rapid and massive cell destruction, as occurs, for example, during chemotherapy for acute leukemia, particularly in children. Its most serious complication is acute renal failure resulting from the deposit of uric acid crystals in the kidney. This severe and sometimes fatal complication necessitates recourse to external dialysis in most cases. Early administration of Fasturtec® enables avoidance of this risk. Discovered by Sanofi-Synthélabo, rasburicase is an enzyme, urate oxidase, obtained by genetic engineering. It permits the conversion of uric acid, poorly soluble and nephrotoxic, into allantoin, a highly soluble compound readily eliminated in the urine. Rasburicase was approved in February 2001 in Europe where it is marketed under the brand name Fasturtec®.
In the U.S., it is in the process of registration and will be marketed under the brand name Elitek®. In Japan, it is in clinical development.
### Cardiovascular / thrombosis

<table>
<thead>
<tr>
<th>Principal products</th>
<th>Compounds</th>
<th>Indications</th>
<th>Consolidated sales (in millions euros)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>1999</td>
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<tr>
<td>Plavix*</td>
<td>clopidogrel</td>
<td>Atherothrombosis</td>
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<td>Aprovel*/Avapro*</td>
<td>irbesartan</td>
<td>Hypertension</td>
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<td>Fraxiparine*</td>
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<td>betaxolol</td>
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**Market ranking:**
- Antiplatelet agents: N°.1 in Europe and N°.1 in the U.S. with Plavix® and Ticlid®
- Angiotensin II antagonists: N°.2 in Europe with Aprovel® and N°.3 in the U.S. with Avapro®
- Injectable anticoagulants: N°.2 in Europe with Fraxiparine®
- Inotropic agents: N°.1 in Europe with Corotrope®, N°.1 in the U.S. with Primacor® and N°.2 in Japan with Milrila®
- Antiarrhythmics: N°.1 in Europe with Cordarone®
- Calcium antagonists: N°.4 in Europe with Tildiem®
- Beta-blockers: N°.4 in Japan with Kerlong®

### Central nervous system

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<th>Consolidated sales (in millions euros)</th>
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<td>Aspégic® and derivatives</td>
<td>lysine acetylsalicylate</td>
<td>Fever, pain</td>
<td>99</td>
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**Market ranking:**
- Hypnotics: N°.1 in Europe with Stilnox® and N°.1 in the U.S. with Ambien®
- Antiepileptics: N°.3 in Europe with Depakine®
- Antipsychotics: N°.3 in Europe with Dogmatil® and Solian® and N°.3 in Japan with Dogmatyl®
Cardiovascular / thrombosis

**Aprovel® / Avapro®**

Irbesartan

Hypertension

Aprovel® belongs to the most recent class of antihypertensives, known as angiotensin II receptor antagonists. It has a potent and specific mechanism of action, blocking the effect of the hormone responsible for vascular constriction and thereby restoring normal blood pressure. Aprovel® and CoAprovel® - a combination of irbesartan and a diuretic, hydrochlorothiazide - offer physicians a wide range of therapeutic options enabling them to adapt the treatment to the needs of each patient and thereby achieve blood pressure control in 90% of cases. A single daily dose is sufficient to achieve effective and lasting control of blood pressure, with a safety comparable to that of a placebo at all doses. This excellent safety profile is particularly important in hypertension as the disease is virtually asymptomatic and compliance with treatment, necessarily long-term, is vital in preventing cardiovascular complications.

Launched in 1997, Aprovel® is marketed in more than 75 countries, including the U.S. under the brand name Avapro®, through agreements with Bristol-Myers Squibb. In Japan, where it has been licensed jointly to Bristol-Myers Squibb and Shionogi, submission of a marketing authorization application is scheduled at the end of 2002. An application requesting extension of its indication to diabetic nephropathy was submitted in Europe and in the U.S. in August 2001.

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**Internal medicine**

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Market ranking:

Urological agents: N°3 in Europe with Xatral®

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**Oncology**

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<tr>
<td>Elostatine®</td>
<td>oxaliplatin</td>
<td>Colorectal cancer</td>
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The ranking is based on the sales achieved.
The ranks indicated for antiplatelet agents, angiotensin II receptor antagonists and hypnotics include 100% of the sales achieved with Bristol-Myers Squibb for Plavix® and Aprovel®/Avapro® and with Pharmacia for Stilnox®/Ambien®

Source for ranking: IMS – twelve months cumulative – December 2001

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**Cardiovascular / thrombosis**

**Aprovel® / Avapro®**

Irbesartan

Hypertension

Launched in 1997, Aprovel® is marketed in more than 75 countries, including the U.S. under the brand name Avapro®, through agreements with Bristol-Myers Squibb. In Japan, where it has been licensed jointly to Bristol-Myers Squibb and Shionogi, submission of a marketing authorization application is scheduled at the end of 2002. An application requesting extension of its indication to diabetic nephropathy was submitted in Europe and in the U.S. in August 2001.
The U.S. health authorities have granted the application a priority review. This application is based on the results of the PRIME program demonstrating that irbesartan protects patients suffering from hypertension and type 2 diabetes from progression of nephropathy, whether early or advanced. The PRIME program, comprising the studies IRMA 2 and IDNT, enrolled over 2,300 hypertensive diabetic patients. In early 2002, the Advisory Committee for cardiovascular and renal drugs of the Food and Drug Administration (FDA) in the U.S. gave a split vote (five against six) on the approvability of this extension of indication. Bristol-Myers Squibb and Sanofi-Synthélabo subsequently withdrew the application for extension of the indication in order to have time to respond to the questions raised, prior to resubmitting the dossier.

In March 2002, the Committee for Proprietary Medicinal Products (CPMP) recommended granting marketing authorization in Europe for irbesartan in the treatment of diabetic renal disease. The I-PRESERVE study, evaluating irbesartan in the treatment of heart failure, should start in 2002. In constant progression, heart failure currently affects 20 million people worldwide, with a five-year mortality rate of approximately 50%.

**Hypertension**

Hypertension is characterized by the raised pressure to which the heart and blood vessels are subjected. The understanding and management of this disease have radically changed over the last few years. The international authorities on the subject (WHO, ISH, JNC) have reached consensus on a new definition of the threshold blood pressure levels beyond which an individual is considered to be hypertensive (140/90 mm Hg). The recommended blood pressures are even lower for patients in whom hypertension is associated with another disorder carrying a high cardiovascular risk, such as diabetes or renal impairment (proteinuria). These authorities also agree in recommending that the treatment of patients should take into account all the risk factors involved. Furthermore, every effort should be made not only to reduce blood pressure levels, but to try to restore these to normal values. These new data imply that physicians should have access to new agents that are highly effective and well tolerated, permitting the continued long-term treatment of patients. Besides the high incidences of both hypertension (20% of the population) and diabetes (5% to 10% of the population depending on the country), 50% of the patients affected present both disorders simultaneously. This association doubles the risk of cardiovascular complications.

**Cordarone® / Ancaron®**

**amiodarone**

Cardiac rhythm disorders

Thirty-five years after its first marketing authorization was granted, Cordarone® remains the reference antiarrhythmic due to its efficacy in preventing the recurrence of rhythm disorders. Cordarone® is effective against supraventricular rhythm disorders, the most common of these being atrial fibrillation, as well as potentially life-threatening ventricular rhythm disorders. The AMIO VIRT study demonstrated that treatment with Cordarone® is as effective as the implantation of defibrillators in the secondary prevention of sudden death due to ventricular arrhythmia. Cordarone® has a good cardiac safety profile for an antiarrhythmic agent as it does not induce complications such as torsade de pointe (a serious and potentially fatal ventricular rhythm disorder) or ventricular failure, which may sometimes result from this type of treatment. However, its effects on thyroid function limit its prescription. Cordarone® is available in more than 110 countries, including the U.S. where it is licensed to Wyeth, and Japan where it is marketed under the brand name Ancaron® by the joint venture with Taisho.
Cardiac arrhythmia
Irrespective of whether they arise in the atria (supraventricular rhythm disorders) or in the ventricles (ventricular rhythm disorders), cardiac arrhythmias generally have a chronic cause and therefore tend to recur. Patients suffering from cardiac rhythm disorders present various symptoms, such as palpitations, malaise and syncope, and may even experience heart failure. The most serious forms may lead to sudden death. The prevalence of atrial fibrillation, the most frequent supraventricular rhythm disorder, is 1% in the population as a whole, but increases with age (exceeding 8% in those more than 65 years old).

Tildiem®
diltiazem
Angina, hypertension
Among calcium antagonists, Tildiem® is considered as the reference treatment for angina. It increases oxygen supply through coronary vasodilatation, while simultaneously reducing myocardial needs by diminishing heart rate and lowering peripheral artery resistance. Tildiem® consequently has good antianginal efficacy, with a good safety profile. The prolonged release formulations of Tildiem® LP 200/300 mg provide 24-hour protection against ischemia with a single daily dose. This ease of use improves compliance, as well as the safety of the treatment. Furthermore, a meta-analysis showed that these formulations permit consistent regulation of heart rate: the higher the initial rate, the more it is reduced by Tildiem®. A study conducted in 1999 showed that the profile of release of Tildiem® LP 200/300 mg is unique in its therapeutic class. The NORDIL study of morbidity and mortality associated with hypertension showed that Tildiem® was as effective as the reference treatment (diuretics and beta-blockers) in reducing cardiovascular complications.

Angina
Angina results from an imbalance between myocardial oxygen demand and supply as a result of constriction of a coronary artery (artery nourishing the heart). It is manifested by intense and distressing chest pain, particularly during effort. Angina is an incapacitating and potentially life-threatening disease. The usual treatment consists in treating the risk factors and prescribing one or more drugs belonging to three different classes: nitrates, beta-blockers and calcium antagonists. This is accompanied by the use of salicylates, known for their cardioprotective properties. Sanofi-Synthélabo has products in each of these therapeutic classes.

Kerlone® / Kerlong®
betaxolol
Hypertension, angina
A cardioselective beta-blocker, Kerlone® restores normal blood pressure with a single daily dose. Kerlone® is marketed in numerous European countries, in the U.S. by the joint venture with Pharmacia, and in Japan under the name Kerlong® by the joint venture with Mitsubishi.
**Corotrope® / Primacor® / Milrila®**
milrinone
Heart failure

Corotrope® combines positive inotropic properties (increasing the contractile force of the heart) with a vasodilatory action. It constitutes an effective treatment for advanced forms of heart failure. It is also a treatment for certain less advanced forms that have been abruptly decompensated by a dietary change or intercurrent disease. Corotrope® is marketed in several European countries, in the U.S. under the name Primacor®, and in Japan under the name Milrila® by the joint venture with Yamanouchi.

**Heart failure**
Related to a defect in the pumping function of the left ventricle, heart failure passes through stages of differing seriousness. Accompanied by breathlessness, edemas and various types of effusion, the most severe forms may render everyday activities practically impossible. The prevalence of heart failure is around 0.3% to 2%, increasing almost exponentially with age.

**Plavix®**
clopidogrel
Atherothrombosis

Plavix®, a platelet adenosine diphosphate receptor antagonist, is designed to prevent atherothrombotic events in patients presenting a history of recent myocardial infarction, recent ischemic stroke or established peripheral arterial disease. Plavix® is the only drug indicated for the secondary prevention of atherothrombosis irrespective of the location of the arteries initially affected (heart, brain, lower limbs). The results of the CAPRIE study, the largest phase III study ever conducted with almost 20,000 patients enrolled, supports the broad indication of Plavix®. This study demonstrated the superior efficacy of Plavix® relative to aspirin, with a safety profile which is at least equally good. Launched in 1998, Plavix® is marketed in over 75 countries, including the U.S., under agreements with Bristol-Myers Squibb. In Japan, where it is being developed in partnership with Daiichi, submission of a marketing authorization application is scheduled in 2004. An application for extension of the indication to acute coronary syndrome was submitted in the U.S. in August 2001 and in Europe in November 2001. After a priority review procedure, the U.S. health authorities approved this extension of the indication in February 2002. The application is based on the results of the CURE study which demonstrated that on top of standard therapy, including aspirin, clopidogrel reduced the risk of atherothrombotic events (myocardial infarction, stroke, cardiovascular death) by 20% and provided significant short- and long-term benefit in patients presenting an acute coronary syndrome. With more than 12,000 patients included, CURE is the largest study ever conducted with patients presenting unstable angina or non-Q-wave myocardial infarction. The vast clinical program on clopidogrel includes over 50,000 patients in four major ongoing studies: MATCH, assessing the benefit of clopidogrel combined with aspirin in the prevention of serious ischemic events in high-risk patients who have recently experienced a stroke; COMMIT, evaluating the benefit of clopidogrel combined with aspirin in myocardial infarction; CREDO, evaluating the benefit of clopidogrel combined with aspirin in the long-term treatment of patients who have undergone coronary angioplasty; and WATCH, assessing the value of clopidogrel in patients suffering from heart failure.
Atherothrombosis
Atherothrombosis constitutes the formation of a thrombus in a vessel damaged by atherosclerosis, a process common to numerous cardiovascular diseases. An atheromatous plaque may become unstable and break up, thereby exposing its components, such as collagen to the circulating blood. This in turn triggers the adhesion of platelets to the site of the injury, initiating the formation of a thrombus.
The thrombus may spread and eventually obstruct the vessel, leading to acute ischemia and tissue damage. The final consequence may be a fatal or non-fatal cardiovascular event, such as stroke, acute coronary syndromes (unstable angina, myocardial infarction with or without Q-wave, vascular death) or arterial occlusive disease of the lower limbs. All these symptoms are ischemic manifestations of the same process, atherothrombosis.
Atherothrombotic events represent the major cause of morbidity and premature death in industrialized countries. Every year, in Europe and the U.S., 3.4 million people experience an acute coronary event and 1.2 million suffer an ischemic stroke. A further 16.8 million present signs of peripheral arterial disease.

Ticlid®
ticlopidine
Thrombosis
Ticlid® is indicated for the prevention of coronary or cerebrovascular ischemic events in patients at risk (following an initial ischemic stroke or transient ischemic attack, or symptomatic peripheral arterial disease). In combination with aspirin, Ticlid® is the standard prophylactic treatment against the risk of thrombosis (reocclusion of the dilated artery) in patients who have undergone coronary angioplasty with insertion of a stent. Ticlid® is marketed in over 75 countries. In the U.S., it is licensed to Roche. In Japan, where it is marketed under the brand name Panaldine®, it is licensed to Daiichi.

Fraxiparine®
nadroparin calcium
Thrombosis
Fraxiparine®, an injectable low molecular weight heparin launched in 1986 is currently marketed in over 100 countries (excluding the U.S. and Japan). The indications of Fraxiparine® have expanded over the years. Initially indicated for the prevention of venous thromboembolic disease, this antithrombotic can now also be prescribed for the treatment of venous thromboembolic disease. It is also used to treat acute coronary syndromes. Fraxodi®, a curative treatment of venous thromboembolic disease, with a single daily injection was launched in France in 1998 and introduced into several countries in Europe and Latin America in 1999 and 2000. This regimen permits shorter hospital stays, facilitates outpatient treatment and favors patient recovery. The new indication of Fraxiparine® in the treatment of the acute phase of unstable angina was successfully registered in several countries in 1999 and 2000, including France, Italy, Portugal and Spain.

Venous thrombosis
Caused by a blood clot leading to occlusion of the vein, deep vein thrombosis (or phlebitis of the lower limbs), and its most serious complication, pulmonary embolism, are responsible for 300,000 to 600,000 hospitalizations every year in the U.S. The frequency of pulmonary embolism increases with age. Often silent, this disease is responsible for numerous unexplained deaths (10% of deaths according to post-mortem statistics in the U.S.).
Central nervous system

**Stilnox® / Ambien® / Myslee®**

Zolpidem

**Insomnia**

Stilnox® rapidly induces sleep which is qualitatively and quantitatively very close to natural sleep, its flexibility of administration permitting a personalized treatment of insomnia. Stilnox® is a non-benzodiazepine hypnotic, possessing a mechanism of action conferring a selective hypnotic activity. Stilnox® rapidly induces a sleep lasting 6 to 7 hours, qualitatively closely resembling natural sleep. It therefore provides a satisfactory therapeutic response to the various symptoms characterizing insomnia (difficulties in falling asleep, early morning awakening and nocturnal awakenings).

At recommended doses, Stilnox® is practically devoid of residual effects after awakening, such as impaired memory, alertness and attention. Furthermore, once the therapeutic objective has been attained, treatment can be discontinued without difficulty in most patients, thereby minimizing the risk of developing dependence.

Stilnox® is currently available in over 75 countries. In the U.S., it is marketed under the brand name Ambien® by Lorex, a joint venture of Sanofi-Synthélabo with Pharmacia. Sanofi-Synthélabo will recover all rights to Ambien® from April 16, 2002, following acquisition of the 51% of Lorex held by Pharmacia.

In Japan, zolpidem is marketed under the brand name Myslee® by the joint venture with Fujisawa. With prescriptions equivalent to nearly 7 billion nights, Stilnox® benefits from a particularly important post-marketing experience in the area of insomnia.

A vast program of clinical trials in Europe and the U.S., including over 4,000 patients suffering from chronic insomnia lasting more than one month, permitted confirmation of the value of a therapeutic regimen for insomnia, based on discontinuous, “as needed” administration. These results represent a major advance, as they demonstrate for the first time that systematic recourse to daily intake of a hypnotic is not the sole treatment option. This alternative represents both an effective and a safe therapeutic strategy.

**Insomnia**

Insomnia constitutes the most frequent sleep disorder, experienced occasionally by 20% to 30% of the population on average and recurrently by 10% of this population. Its impact on health and its cost to society are now better known. Insomnia is manifested principally by three symptoms, which are most often associated: difficulty in falling asleep, problems maintaining sleep and, finally, early morning awakening. However, the symptoms of insomnia are not limited to the night. Insomnia also has numerous daytime consequences, such as mood alterations, difficulties in concentrating and memory disorders, as well as impaired alertness and attention.

The treatment of insomnia is based on an evaluation of both its causes and the factors perpetuating it. The therapeutic approach includes patient education in the rules of sleep hygiene to be observed and, when necessary, the prescription of a hypnotic adapted to each patient. Emphasis is placed on the necessity of administering the hypnotic for short periods only, or discontinuously, avoiding unnecessarily prolonged treatments and prophylactic use in order to prevent the development of dependence.
**Depakine®**
Sodium valproate
Epilepsy

Depakine® is a broad-spectrum antiepileptic prescribed successfully for over 30 years. Numerous clinical trials, as well as long years of experience have abundantly shown that Depakine® is effective in all types of epileptic seizure and epileptic syndrome, and is generally well tolerated. Depakine® consequently remains a reference treatment for epilepsy worldwide. Furthermore, Depakine® does not induce paradoxical aggravation of seizures. The Chrono form (prolonged release formulation) permits once daily administration, thereby improving compliance with treatment and overall management of the patient. Depakine® is available in a wide range of formulations, permitting its adaptation to all types of patients. New pharmaceutical forms, facilitating in particular the use of Depakine® in children and the elderly, are in development. Depakine® is marketed in over 100 countries, including the U.S., where it is licensed to Abbott.

**Epilepsy**
Epilepsy is a frequent, chronic neurological disorder, affecting approximately 1% of the population worldwide. Children under 10 years old and the elderly are those most frequently affected. Epilepsy is characterized by repeated spontaneous seizures resulting from an excessive discharge of cerebral neurons. The characteristics of these seizures and their repercussions (including physical injury, loss of self-confidence and even decreased autonomy), their origin, the presence or absence of associated symptoms and the quality of response to treatments make this a heterogeneous disorder. Our understanding of epilepsy is improving with recent progress in genetics and cerebral electrophysiology, and also thanks to new techniques of functional cerebral imaging. It is crucial to facilitate access to care, including diagnosis, treatment and counseling.

**With adequate treatment, the vast majority of epileptic patients can continue to live a normal, productive and fulfilling lives.**

**Dogmatil® / Dogmatyl®**
sulpiride
Neurotic and psychosomatic disorders

At low doses, Dogmatil® 50 mg is used in numerous countries for the symptomatic treatment of neurotic and/or psychomatic disorders. Its mechanism of action on central and peripheral dopaminergic receptors permits rapid improvement of the psychic state of the patient as well as relief of functional symptoms in patients difficult to treat. At higher doses, Dogmatil® 200/400 mg is also proposed for the treatment of psychotic states. Its good cardiovascular and neurological safety profile makes it particularly suitable for the treatment of elderly patients.

Dogmatil® is available in over 90 countries, including Japan, where it is marketed under the brand name Dogmatyl® by the joint venture with Fujisawa.

**Neurotic and psychosomatic disorders**
Patients suffering from these disorders present a variety of somatic disorders, associated with psychological distress. Clinical investigations generally fail to reveal any organic cause. The treatment of these patients is problematic, with a frequent risk of self-medication, as well as a high rate of prescription for complementary tests.
Solian®

amisulpride

Schizophrenia

The originality of the pharmacological profile of this atypical antipsychotic is based on its capacity to act selectively on D₃/D₂ dopaminergic receptors and its dual pre- and post-synaptic activity. Furthermore, its preferential action on the limbic system confers excellent neurological safety.

Solian® is effective for all symptoms of schizophrenia, both positive and negative, irrespective of the phase of the disease, whether acute or chronic. At doses of 400 mg to 800 mg per day in patients with positive symptoms and associated depressive symptoms, and at the optimal daily dose of 100 mg in patients with dominant negative symptoms, the efficacy of Solian® is accompanied by a very good safety profile. Solian® is available in the principal European markets.

Aspégic®

Lysine acetylsalicylate

Fever, pain

Aspégic® is a salicylate with the original property of total and immediate solubility. This characteristic confers very rapid efficacy as an analgesic, antipyretic and anti-inflammatory agent, and good gastric safety.

Aspégic® is marketed in certain countries in Europe, Africa and the Middle East.

Internal medicine

Xatral®

alfuzosin

Benign prostatic hyperplasia

Xatral® acts on the symptoms of benign prostatic hyperplasia. Taking effect from the first dose onwards, it maintains its efficacy over the long term, preserves patient quality of life, respects their sexual activity and diminishes the onset of serious complications, such as acute urine retention.

Xatral® is the first marketed alpha₁-blocker capable of acting selectively on the urinary system. This uroselectivity confers efficacy right from the start, without any dose titration, as well as a good safety profile, particularly from the cardiovascular standpoint, confirmed by extensive clinical experience. Long-term follow-up of patients has shown that the improvement of mictional disorders achieved by Xatral® has a favorable effect on quality of life, respecting sexual activity.

Besides this symptomatic action, preliminary clinical results have shown a low rate of complications, such as acute urinary retention, in patients treated with Xatral®. These positive results may be explained by the favorable action of Xatral® on intravesical pressure, an index of occlusion, as well as on postmictional residual volume. An extensive program of prospective clinical studies is currently ongoing in Europe.

Schizophrenia

A particularly severe and incapacitating disorder, schizophrenia affects approximately 1% of the population. It generally first appears during adolescence or early adulthood. In the majority of cases, the disease follows a chronic course, necessitating long-term treatments and frequent recourse to hospitalization. Two principal types of symptoms are distinguished, which may coexist or appear at different stages of this progressive disease, acute or chronic:

- positive symptoms, notably delusions and hallucinations, most often occur during the acute phase;
- negative symptoms, characterized by introversion and an incapacity for action, appear very early on or during the chronic phase of the disease and lead to the progressive social isolation of the patient.
and the U.S. for the treatment of acute urinary retention and its prevention. The new once-daily formulation of Xatral® was developed to improve the safety of the product and compliance with treatment. Once-daily Xatral® is registered in over 65 countries and is marketed in 12 European countries and in more than 30 other countries. Registration is ongoing in the U.S., where an Approvable Letter was received in October 2001 from the health authorities, following submission of a marketing authorization application in December 2000. The product will be marketed in the U.S. under the brand name UroXatral®.

**Benign prostatic hyperplasia**
Benign prostatic hyperplasia is a very frequent disorder, responsible to a variable degree for urinary symptoms in almost half the male population aged over 60 years. These urinary disorders, not correlated with prostate volume, may have a considerable impact on the quality of life of the patients. Although the disorder is benign in the majority of cases, in the long term it may nevertheless give rise to serious complications, such as acute urinary retention, which may necessitate surgery. Certain risk factors have been identified, such as increased postmictional residual volume and prostate volume. The objectives of treatment of benign prostatic hyperplasia comprise rapid symptom relief, restoration of patient quality of life and management of the long-term effects of the disorder.

**Oncology**

**Eloxatine®**
oxaliplatin
Colorectal cancer

An innovative anticancer agent, this platinum derivative constitutes a crucial therapeutic advance. The only platinum derivative active in the treatment of metastatic colorectal cancer, it permits, when administered in combination with 5-fluorouracil, doubling of the remission rate, a 50% improvement in progression-free survival of patients, and achievement of a median overall survival rate of more than 16 months. Furthermore, this significant progress is obtained without any degradation of the quality of life of the patients. The ability of Eloxatine® to reduce the size of hepatic metastases makes it possible to operate on patients for whom surgery had previously been excluded, providing hope of prolonged survival, which may reach or even exceed 5 years in 30% to 40% of cases. The only agent for which this feature has been demonstrated so far, Eloxatine®, in this respect, plays a key role in the development of new therapeutic strategies. Eloxatine® is marketed as a first-line treatment in Europe, as well as in numerous countries in Asia and Latin America.

In the U.S., Sanofi-Synthélabo chose to conduct further clinical investigation, agreed with the health authorities, in order to obtain registration for second-line treatment; the application for marketing authorization will be submitted mid-2002. A clinical study evaluating Eloxatine® in the adjuvant treatment of colorectal cancer is also ongoing. Furthermore, the application for marketing authorization in ovarian cancer will be submitted in Europe by the end of 2002.

**Colorectal cancer**

With a million new cases diagnosed every year, colorectal cancer is a major cause of morbidity and mortality. It affects both sexes, with a frequency close to that of non-small-cell lung cancer in men, and breast cancer in women. The 5-year survival rate for all stages taken together, is still only 40% and more than 500,000 patients die each year. Surgery remains a major therapeutic strategy and alone permits the treatment of approximately half the patients. However, metastases may develop after resection of the primary tumor. Moreover, numerous patients already have a highly advanced cancer and/or metastases on diagnosis. In this case, chemotherapy constitutes the first-line, if not the only therapeutic option.
Chemical manufacturing

In 2001, strong growth in sales of Plavix® and Aprovel® ensured optimal utilization of capacity at the new production facilities for clopidogrel (Sisteron, France) and irbesartan (Aramon, France), which came into operation in 2000.

Further investment has been committed both on the industrial front, to build new production capacity, and in research and development, to identify and optimize synthesis techniques.

The industrial investment program is designed to ensure that the group, through its own facilities or those of partner companies, has a number of separate sites capable of producing the principal compounds using various sources, in strict compliance with safety standards and good manufacturing practice.

In 2001, the Sisteron facility (France) was approved to handle part of the production of fondaparinux sodium for the American market.

Pharmaceutical manufacturing

2001 saw a continuation of the multisourcing industrial strategy, designed to safeguard supplies of the group’s key products by splitting production between at least two facilities.

Substantial investment in increased capacity, based mainly in Europe, has been approved and is now under way. This investment program covers both dry and injectable formulations, and will also improve quality and safety standards.

The sale of the facility at Coutances (France) to Unither has been completed, and the transfer of the liquid and paste formulations manufactured there to other group sites will take place over the next two years. The sale of the Tires facility (Portugal) to Sofarimex was also completed in 2001.

2001 also saw the approval of a number of facilities for the manufacture of products intended for the American market. The Tours facility (France) was approved for the production of Ambien® and UroXatral®, and the facility at Notre-Dame de Bondeville (France) for Primacor®.

Pharmaceutical distribution

There were major changes in the distribution function during 2001, in particular the refocusing of French distribution activities on three sites, coupled with investment in information systems and processes to allow for back-up between the northern and southern sites.

On the international front, a number of quality initiatives were implemented, designed to further enhance the standard of customer service offered by the group.
“Determination and cooperation: our international organization”

The number and quality of the drugs originating from its research have led Sanofi-Synthélabo to reinforce its international presence and pursue an aggressive policy of capturing market share.

+36% in the U.S. in developed sales and +55% in operating profit: the acceleration in Sanofi-Synthélabo’s growth testifies to its firm foothold in the world’s leading pharmaceutical market.

+10% in Japan: Sanofi-Synthélabo has further increased its presence in this country thanks to an active partnership policy. Its objective is to strengthen its direct presence.

Étienne Jacob  
Senior Vice President  
Europe (except France)

Gordon Proctor  
Senior Vice President  
North America

Yves Bruslon  
Vice President  
Latin America and Africa

Antoine Ortoli  
Vice President  
Asia, Eastern Europe and Middle East

Philippe Fauchet  
General Manager  
Japan
In 2001, Sanofi-Synthélabo achieved higher sales growth than the pharmaceuticals market, both worldwide and in each of the major markets. The main drivers of this growth were the three blockbusters, Plavix®, Stilnox® and Aprovel®, backed by strong contributions from Eloxatine®, Fraxiparine®, Depakine® and Xatral®.

Sales by geographic area

<table>
<thead>
<tr>
<th></th>
<th>Consolidated sales</th>
<th>Developed sales</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(in millions of euros)</td>
<td>Growth</td>
</tr>
<tr>
<td>Europe</td>
<td>3,756</td>
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<tr>
<td>U.S.</td>
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<td>+28%</td>
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<tr>
<td>Canada, Puerto Rico</td>
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<td>+12%</td>
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<tr>
<td>Japan</td>
<td>419</td>
<td>+10%</td>
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<td>Latin America</td>
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<tr>
<td>Pharmaceutical products</td>
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<tr>
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</tr>
<tr>
<td>Total</td>
<td>6,488</td>
<td>+15%</td>
</tr>
</tbody>
</table>

Growth figures are on a comparable basis. Sales of pharmaceutical products comprise sales generated by the ethicals, OTC and generics businesses. Developed sales includes 100% of the sales generated under the agreements with Bristol-Myers Squibb and Pharmacia.

Europe

France
Consolidated sales of pharmaceutical products: 1,414 million euros
Market share: 7.9%
Ranking: No.2

Enforced price cuts for products judged by the Commission de la Transparence to have inadequate medical benefits once again had a significant impact in 2001. In addition, recently-launched, innovative products, including Aprovel®, were affected by price cuts that took effect in October. Aprovel® posted a sharp rise in sales, increasing its share of the highly competitive angiotensin II receptor antagonists market to 24.7%. Sales of Tildiem® leveled out, while sales of Cordarone® fell slightly.

There was further confirmation of the excellent performance of Plavix®, while sales of Ticlid® continued to fall. Nevertheless, overall sales advanced very strongly, confirming Sanofi-Synthélabo’s leading position in the atherothrombosis market. Sales of Fraxiparine® slipped back in the face of intense competition. Stilnox® reported growth ahead of that in the hypnotics market generally, confirming its position as market leader. There was further growth in sales of Depakine®, which remained N°.1 in the anti-epileptics market. Sales of Solian® were sharply higher.

Sales of Xatral® rose, boosted by the previous year’s launch of the once-daily formulation. Eloxatine® reported a strong advance in sales. Sales of the Aspégic® range also increased. Laboratoires Irex, the French generics subsidiary, saw a decline in sales.
Germany
Consolidated sales of pharmaceutical products: 593 million euros
Market share: 2.8%
Ranking: No.11

The authorities continued their policy of curbing healthcare costs, in particular by favoring parallel imports and generics.
The main drivers of growth were Plavix®, Aprovel®, Eloxatine®, Fraxiparine®, Xatral® and Solian®. Sales of Cordarone® were sharply down due to competition from generics.
Fasturtec® was launched in May.
Lichtenstein Pharmazeutica, the German generics subsidiary, posted fine sales growth in a favorable environment.

Italy
Consolidated sales of pharmaceutical products: 429 million euros
Market share: 3.1%
Ranking: No.10

M easures to restrict healthcare spending, especially by favoring generics, were implemented in September. This was accompanied by an enforced price cut of 5% for all patent-expired products.
The success of Aprovel® and Eloxatine® was confirmed. Sales of Fraxiparine® rose sharply, lifted by the removal of restrictions on the reimbursement of low molecular weight heparins in February. Sales of Xatral®, the once-daily formulation of which was launched in May, were substantially higher, as were those of Depakine®.
Stilnox® and Solian® recorded further growth, while sales of Ticlid® fell under competition from generics.
A decision to add Plavix® to the reimbursable drugs list is still pending.

Spain
Consolidated sales of pharmaceutical products: 295 million euros
Market share: 2.8%
Ranking: No.10

The Spanish subsidiary achieved growth ahead of the pharmaceuticals market, despite the policy of curbing healthcare costs by favoring generics.
The success of Plavix® was confirmed. Strong growth in sales of Aprovel® took its market share to 22.4%. Eloxatine®, launched the previous year, turned in an excellent performance. Fraxiparine® also recorded stronger sales, thanks in particular to a price increase effective from March. Sales of Xatral® also rose, but Ticlid® saw a sharp decline. Fasturtec® was launched in January 2002.

United Kingdom
Consolidated sales of pharmaceutical products: 267 million euros
Market share: 2.6%
Ranking: No.10

Growth of the UK operations was strong, ahead of the pharmaceuticals market.
The success of Plavix®, the main driver of growth for the subsidiary, was confirmed. Depakine® performed well, thanks to the February launch of Depakote®. Sales of Solian® rose very sharply, due largely to the launch of the new drinkable solution formulation in September. Sales of Xatral® also advanced, helped by the previous year’s launch of the once-daily formulation.
The performance of Aprovel® in the UK market reflects the product’s success among physicians.
CoAprovel® was launched in January. Sales of Tildiem® fell, under competition from generics.
Eloxatine® recorded further growth. Fasturtec® was launched in May. Sterwin Medicines, the UK generics subsidiary, recorded a decline in sales.
Belgium
Consolidated sales of pharmaceutical products: 134 million euros
Market share: 4.5%
Ranking: No.5

In June, the authorities instituted a reference price system for patent-expired products, including Tildiem® (non sustained-release form), Ticlid®, Cordarone® and Dogmatil®. The main driver of growth for the subsidiary was Plavix®, which obtained reimbursable drug status in March. Sales of Aprovel® were sharply higher, and Fraxiparine® sales also rose slightly. Stilnox® registered good sales figures.

Portugal
Consolidated sales of pharmaceutical products: 78 million euros
Market share: 3.6%
Ranking: No.7

The success of Aprovel® was confirmed, while Solian®, Stilnox® and Xatral® all performed well. Sales of Fraxiparine® and Ticlid® advanced slightly, but Tildiem® and the Aspégic® range saw a decline in sales. A decision to add Plavix® to the reimbursable drugs list is pending. Fasturtec® was launched in September.

Switzerland
Consolidated sales of pharmaceutical products: 75 million euros
Market share: 3.4%
Ranking: No.7

A new method of paying dispensing chemists, cutting the price to the public of costly drugs and raising the price of cheaper drugs, was introduced in July. It applies only to reimbursed prescription medicines. This new method favored generics, as did the decision to allow dispensing chemists to substitute generics for branded drugs. The success of Aprovel® and Plavix® was confirmed. Eloxatine® secured reimbursable drug status in January. Sales of Fraxiparine®, Stilnox® and Depakine® all advanced. The authorities have decided to implement measures during 2002 to facilitate parallel imports and price cuts.

Poland
Consolidated sales of pharmaceutical products: 73 million euros
Market share: 2.5%
Ranking: No.12

There was significant growth in sales of Fraxiparine®, which maintained its strong position in the hospital sector and achieved greater penetration in the non-hospital sector, especially after Fraxodi® was launched in September. Depakine® performed well, lifted by the launch of the Chrono formulation for the treatment of bipolar disorders in September. Sales of Xatral® advanced strongly, boosted by the release of the once-a-day formulation in September.
Scandinavia
Consolidated sales of pharmaceutical products:
73 million euros
Market share: 1.4%
Ranking: No.19

In Sweden, Sanofi-Synthélabo bought out AstraZeneca's 50% interest in the Swedish joint venture. The Group now controls 100% of this entity, which handled the marketing of products including Stilnox® and Xatral®.
The main drivers of growth at the Swedish subsidiary were Plavix®, Aprovel® and Eloxitine®.
Fasturtec® was launched in September.

In Finland, growth was mainly fuelled by Eloxitine®, Plavix®, and Stilnox®. The once-a-day formulation of Xatral® was launched in September.
Plavix® obtained reimbursable drug status in November.
Fasturtec® was launched in September.

In Norway, the authorities imposed price cuts on some products in June.
Although affected by these measures, Aprovel®, the Norwegian subsidiary's best-selling product, still recorded an excellent performance.
Sales of Plavix® and Eloxitine® advanced very strongly.
Fasturtec® was launched in September.

In Denmark, growth was driven by Aprovel®, Plavix® and Stilnox®.
Fasturtec® was launched in September.

Greece
Consolidated sales of pharmaceutical products:
73 million euros
Market share: 3.6%
Ranking: No.11

The success of Plavix® and Aprovel® was confirmed, and CoAprovel® was launched in October. Tildiem®, the Greek subsidiary's best-selling product, recorded an increase in sales. Eloxitine® performed extremely well. Fasturtec® was launched in September.

Turkey
Consolidated sales of pharmaceutical products:
71 million euros
Market share: 2.0%
Ranking: No.17

In challenging economic conditions, sales in Turkey fell slightly on a comparable basis. Reported sales fell significantly due to the very sharp devaluation of the national currency.
In April, the authorities imposed price cuts on imported products.
Plavix® and Aprovel®, launched in the previous year, recorded excellent performances.

Hungary
Consolidated sales of pharmaceutical products:
59 million euros
Market share: 6.3%
Ranking: No.4

Sales of Fraxiparine®, of which the Fraxodi® form was launched in November, were higher but sales of Ticlid® fell. Plavix® and Aprovel® were launched in July.

Netherlands
Consolidated sales of pharmaceutical products:
54 million euros
Market share: 1.9%
Ranking: No.16

The success of Aprovel®, the Dutch subsidiary's best-selling product, was confirmed. There were excellent performances from Plavix®, Fraxiparine® and Eloxitine®, which benefited from a price
increase in March. Sales of Xatral® and Tildiem® also advanced. Sales of Depakine® were stable, due largely to a cut in the price of the Chrono formulation in March. Fasturtec® was launched in September.

**Czech Republic**
Consolidated sales of pharmaceutical products: 32 million euros  
Market share: 3.7%  
Ranking: No.4

Sales of Kerlone® advanced strongly. Fraxiparine® turned in an excellent performance, thanks in particular to the launch of Fraxiparine® Forte in January. Eloxatine®, which became available to Czech patients in the previous year on a named patient basis, also performed well. Plavix® was launched in May.

**Austria**
Consolidated sales of pharmaceutical products: 29 million euros  
Market share: 1.7%  
Ranking: No.18

The main driver of growth was Plavix®. Sales of Solian®, Eloxatine®, Xatral® and Stilnox® advanced strongly. Plavix® was launched in May.

**North America**

**United States**
In 2001, Sanofi-Synthélabo further strengthened its presence in the U.S.:
- The contribution of the U.S. to developed sales reached 36%, compared with 31% in the previous year;
- The contribution of the U.S. to Group operating profit was 41%, against 34% in the previous year;
- The number of medical sales representatives rose to 2,068, compared with 1,155 in the previous year.

During 2001, the Group’s products were marketed:
- By its subsidiary, Sanofi-Synthélabo Inc;
- Via an alliance with Bristol-Myers Squibb, for Plavix® and Avapro®;
- Via the Lorex Pharmaceuticals joint venture, owned 49% by Sanofi-Synthélabo and 51% by Pharmacia, for Ambien® and Kerlone®;
- Under license agreements, in the case of Cordarone®, Depakine® and Ticlid® in particular.

The success of the three blockbusters was confirmed in 2001. Plavix® recorded local sales of 1,189 million dollars, up 49%, confirming its No.1 position in the platelet anti-aggregants market. Under the agreements with Bristol-Myers Squibb, these sales are not consolidated by Sanofi-Synthélabo. Avapro® generated sales of 351 million dollars, up 49%, and ranks no.3 in the angiotensin II receptor antagonists market with a 17.7% share. Under the agreements with Bristol-Myers Squibb, these sales are not consolidated by Sanofi-Synthélabo. In accordance with an agreement signed in June, Sanofi-Synthélabo has been handling 50% of the promotional effort for Avapro® since October, compared with 30% previously, with an increase of its share of the profits. In addition, the overall promotional effort for this product has been stepped up significantly, and this should raise its market share towards the levels seen in Europe. Local sales of Ambien® were 900 million dollars, up 28%, consolidating the product’s position as market leader in hypnotics. These sales were 49% consolidated by Sanofi-Synthélabo. Pharmacia will retain 51% of Lorex Pharmaceuticals until April 16, 2002, when Sanofi-Synthélabo will exercise its right to buy out Pharmacia’s stake.

In February 2002, Arixtra®, the Group’s fourth blockbuster, was launched. It is being marketed via a 50-50 joint venture with Organon.

In order to enhance the promotional effort for Avapro®, and in anticipation of the takeover of the entire promotion of Ambien®, the launch of Arixtra® in early 2002 and the strengthening of promotional efforts for Plavix® in 2002, Sanofi-Synthélabo initiated a sales force recruitment drive in the U.S. in mid-2001. This program was successfully implemented, and
the target of increasing the Sanofi-Synthélabo U.S. sales force to 2,000 people by the start of 2002 was achieved. The sales force is now organized into three networks serving primary care physicians and five networks serving medical specialists, responsible for handling:

- The promotion of Ambien®;
- The co-promotion of Plavix® and Avapro® with Bristol-Meyers Squibb;
- The co-promotion of Arixtra® with Organon;
- The promotion of the subsidiary’s products, in particular Hyalgan®.

In January 2002, Eligard® 7.5mg (leuprolide acetate for monthly subcutaneous injection) was approved for the treatment of advanced prostate cancer.

In May 2002, the patent for Primacor® (milrinone), which recorded sales of 181 million dollars in 2001, will expire. The registration process is ongoing for Elitek® (rasburicase) in an indication for hyperuricemia induced by chemotherapy in malignant diseases, and UroXatral® (once-a-day alfuzosin) in the treatment of benign prostate hyperplasia. The new drug application for Eloxatine® (oxaliplatin) as a second-line treatment for colorectal cancer is due to be filed in mid-2002.

Japan

In Japan, the Group’s products are sold through joint ventures and under license agreements with:

- Daiichi for Ticlid® (sold under the name Panaldine®);
- Fujisawa for Stilnox® (sold under the name Myslee®) and Dogmatil® (sold under the name Dogmatyl®);
- Mitsubishi for Kerlone® (sold under the name Kerlong®);
- Taisho for Cordarone® (sold under the name Ancaron®);
- Yamanouchi for Corotrope® (sold under the name Milrila®).

Despite a generally challenging economic environment, Sanofi-Synthélabo achieved consolidated sales growth in Japan well ahead of the pharmaceutical market on a comparable basis. The main growth driver was Myslee®. Launched in December 2000, Myslee® has in just one year won 12.5% of the hypnotics market, where it now ranks second. Stronger sales of Kerlong® and Ancaron® also contributed to the positive trend seen in 2001. Sales of Dogmatyl® were stable. The authorities plan to implement price cuts in April 2002.

Latin America

In Mexico, the subsidiary recorded very strong growth, with sales reaching 127 million euros.

In Brazil, the market was stable in value terms, but there was rapid growth in generics. The subsidiary reported modest growth on a comparable basis, to 109 million euros.

In Colombia, where sales totaled 41 million euros, the subsidiary strengthened its position in an expanding market thanks to the performances of all the strategic products and of the major ethical products. During 2001, a range of products was acquired and a generics company taken over.

In Argentina, sales amounted to 25 million euros in a difficult economic environment.

In Venezuela, very strong growth in sales, to 23 million euros, resulted in market share gains.

Asia / Middle East

In China, against a backdrop of restrictions on healthcare spending, sales consolidated by Sanofi-Synthélabo came to 34 million euros, giving modest growth on a comparable basis. Very strong growth in Group products such as Eloxatine® and Fraxiparine® was offset by a marked decline for the generics range. Aprovel® was launched in January and Plavix® in October.

In Australia, sales were sharply up at 70 million euros, thanks largely to further success for Plavix® and Aprovel®.
In **South Korea**, sales advanced strongly to 44 million euros thanks to the growth of Plavix® and Aprovel®, despite restrictions on healthcare spending.

In **Taiwan**, despite tight controls on healthcare spending, sales consolidated by Sanofi-Synthélabo were significantly higher at 41 million euros, thanks largely to excellent performances by Stilnox®, Aprovel® and Eloxiatine®.

In the **Philippines**, sales recorded very strong growth to 39 million euros, due in particular to rising sales of Plavix®, Aprovel® and Lactacyd®, the subsidiary’s best-selling product.

Sales rose substantially in the Middle East, mainly in **Saudi Arabia** and **Israel**.

**Africa**

Overall, sales in the region were slightly higher, with contrasting trends from country to country.

In **South Africa**, sales rose sharply to 22 million euros, thanks to the performances of Depakine® and Stilnox®.

In **Morocco**, sales consolidated by Sanofi-Synthélabo held steady at 80 million euros in a declining pharmaceuticals market.

In **Algeria**, sales remained stable at 32 million euros.

In **Tunisia**, sales advanced in line with the pharmaceuticals market.

**Central and Eastern Europe**


Against a backdrop of constant reform, **Russia** showed the strongest growth in the region, posting sales of 56 million euros, thanks not only to major Group products like Depakine®, Fraxiparine® and Cordarone® but also to local products such as No-Spa®, the subsidiary’s best-selling product.

All other countries benefited from the recovery, including **Romania** and the **Ukraine**, which had shown signs of economic instability in the previous year.

Source of market data:
IMS and GERS – Twelve month cumulative – December 2001
“Openness and generosity: our ethical principles”

Serving patients, respecting cultures, acting transparently: these are the values which have always guided our communications policy.

80 countries carry out group communication actions in their respective languages.

3,000 press articles about the group throughout the world in 2001.

+350 humanitarian associations or organizations supported worldwide.
Group communications policy is geared to three major objectives:
• informing the public about major disease risk prevention issues
• informing about the major new medicines from our R&D
• building our corporate image with the public and the quality of our financial information with investors.

A network of communications managers in the various sites and countries adapts our communications policy to their local situations and enables Sanofi-Synthélabo to communicate in real time in more than 20 languages.

Group values are also expressed through an active policy of humanitarian sponsoring geared to healthcare.
In 2001, a wide-reaching project was launched to combat malaria.

Supporting the Sanofi-Synthélabo image throughout the world

Through continuous contacts with medical, trade, financial and mainstream press, as well as press releases issued to mark major events (over 30 at corporate level in 2001), regular meetings with business investors, the Letter to Shareholders and a variety of other actions, the high visibility of the group is ensured worldwide. All documents are relayed by the network of local communication managers, translated into the local languages and adapted, as appropriate, to the national context.

The same principles are applied to internal communication, with the bimonthly issue of a magazine, The Blue Dolphin, distributed to all the employees of the group in their own language.
Certain pages are reserved for the individual affiliates to complete the information at a national level.

In 2001, communication efforts were mainly focused on the development of the intranet network, and the re-launch of the internet site. This new version of the website, considerably enriched with information on the major diseases, research areas and products, is easy to access and updated in real time, and has been online since February 2002. The site includes pages reserved for the affiliates to develop their own communication, coordinated with that of the group.

**Educating to prevent disease**

Distributing comprehensive information to the general public designed to help prevent those major diseases in which the group is specialized is one of the traditions of Sanofi-Synthelabo. Initiated over ten years ago, this policy was pursued in 2001 with participation in a public awareness campaign, conducted on a European level, on the risks associated with sleep disorders. Another campaign was devoted to arterial diseases, highlighting the premonitory signs and guidelines for a healthy lifestyle. This campaign will be expanded in 2002.

**Providing information on our products**

The results of clinical studies conducted on new products from research, or on medicines already on the market, are regularly presented at international medical congresses and in the media. In 2001, the principal communications highlighted:

• the efficacy of clopidogrel in the prevention of vascular events in high-risk patients (the CURE study) – 50th scientific sessions of the American College of Cardiology in Orlando, Florida, in March;

• the benefit of irbesartan for hypertensive patients suffering from type 2 diabetes (the PRIME program) – 16th annual congress of the American Society of Hypertension in San Francisco in May;

• the superiority of Arixtra® in the prevention of venous thrombosis after orthopedic surgery - XVIIIth congress of the International Society on Thrombosis and Haemostasis in Paris in July.

The results of these studies were published in the New England Journal of Medicine and The Lancet.

**Placing the group’s expertise at the service of the most vulnerable populations**

Ever since its creation, Sanofi-Synthelabo has been committed to supporting humanitarian actions.

As a partner of Reporters sans frontières, Sanofi-Synthélabo marked the 15th anniversary of the organization with this campaign, which received the Special Jury Prize awarded by CB News at the 2001 Empreintes awards in France.
Worldwide in scope, this approach has been implemented through partnerships with associations or organizations devoted to the populations most in need, notably children. Besides providing financial support, it is based on sharing the group’s expertise concerning healthcare, and on the active participation of its employees. UNICEF, Mécénat Chirurgie Cardiaque, PlaNet Finance, Culture à l’Hôpital, L’Envol and the French Federation for Brain Research are some of the numerous associations long supported by the group.

Our affiliates have taken many initiatives which confirm our commitment to serving the cause of life. These include:
- giving hospitals a human dimension – Fun Centers in Brazil;
- helping children in difficulty – Deutsches Zentrum für Herzkranke Kinder;
- working in Mexico for children with leukemia – Asociación de ayuda a niños con cancer;
- helping children with cardiac problems- Cardiac Children’s Foundation of the Republic of China.

An ambitious project to combat malaria is currently in progress (see the interview with the Chairman). This challenge, commensurate with the size of the group, currently involves thirty employees full time. This project has three aims: making current treatments available, proposing new therapeutic solutions and training healthcare professionals and the general public in Africa.

This association, founded 10 years ago and financed by Sanofi-Synthélabo and by the voluntary contributions of its employees throughout the world, provides support to any employee’s child accidentally injured in the course of their everyday activities, as well as to the child’s family. Intended for the good of all, it operates and increases in strength each year through everyone’s joint efforts.

The association has helped more than 10,000 children of employees worldwide, enabling 250 Vietnamese children to gain access to hospital or other treatment and more than 200 Hungarian children to be vaccinated against hepatitis B. Needless to say, the association is in the forefront in emergency situations, intervening after the earthquakes in Colombia and Turkey in 1999 and, more recently, the floods in Algeria.

A further material proof of Sanofi-Synthélabo’s commitment to health, this association, a pioneering initiative at the time of its creation, is also evidence of a dual solidarity: on the part of the company towards all its employees and among its employees themselves.
“Vitality and synergy: our human resources policy”

Stimulate professional development, encourage training and mobility, propose opportunities, recognize talents, focus energies toward a common goal and enable employees to share in the company’s achievements: the success of Sanofi-Synthélabo involves the dynamic and motivational management of its 30,514 employees. A decentralized organization permits incorporation of the human resources policy in the key responsibilities of line managers and facilitates open discussion.

4,903 new employees.
1,000 additional medical sales representatives in the U.S.
61% of employees outside France.

This fresco was created in real time during an international seminar, showing the values which inform the work of the group’s Human Resources Managers.
Decentralize responsibilities

The diversity of social contexts in the different countries has led Human Resources Management to adopt a decentralized mode of operation. The Corporate Human Resources Department defines the general policy, priorities and principles of management according to Sanofi-Synthélabo’s development strategy. Implementation of this policy is entrusted to the Human Resources departments of the different sectors of activity, countries or sites, which are then responsible for adapting and completing this to suit their specific environment. This organization reduces the time required for decision and action and promotes a social dialogue directly relevant to local realities.

Adapt organizations

In the context of its redeployment in France, Sanofi-Synthélabo decided, at the end of 2000, to transfer its distribution activity at the Ris-Orangis site (France) and the pharmaceutical manufacturing activity at the Coutances site (France) to other sites of the group. These projects were accompanied by the same measures as those implemented at the time of the merger: transfers within the group, company early retirement measures, encouragement of personal projects, etc. with the overall objective of leaving nobody alone to face the problem of his or her future employment. Furthermore, in the particular case of the Coutances facility, the proactive approach of the group favored reindustrialization through durable pharmaceutical activities.

Develop employment

In 2001, a total of 4,903 persons were recruited overall, all countries and functions combined. External recruitments are the responsibility of the units concerned. They are implemented after the wishes of internal mobility expressed by the employees have been examined and they take into account the employee age distribution in each country.
The recruitments were distributed as follows:

1,000 sales representatives recruited in the U.S. in less than six months.

- Exploit the full potential of Plavix® and Avapro®, take over direct responsibility for Ambien®, launch Arixtra... the program of Sanofi-Synthélabo in the U.S. for 2002 called for a change in scale of the sales force. The objective was to recruit 1,000 medical sales representatives, i.e. to double the sales force in 2001.

- As this challenge could not be met using conventional approaches within the time frame of barely five months, from August to December, taking into account the lead times for preparation, the group turned to the internet to cover the whole of the United States.

- A dedicated website was opened and advertised in the press. 31,334 candidatures were received and 12,223 applications were retained on the basis of replies to a detailed questionnaire. Telephone interviews were conducted by a recruitment agency to assess the candidates and select 5,000 of them. Sanofi-Synthélabo management then took over, and local managers personally proceeded to conduct 2,500 individual interviews. A total of 1,088 candidates were finally retained and trained for 15 days in three training centers.

Remunerate the function and the performance

Remuneration has a triple aim: recognition of individual and collective performances, promotion of internal equity and integration of the imperatives of competitiveness relative to the external employment market. Each country adapts this principle according to local practices and realities, with the objective of achieving remuneration levels above the market median. Some employees benefit from a variable personal incentive bonus as part of their remuneration. This may represent up to a third of the total remuneration depending on the nature of the function and the level of responsibility. Its actual amount depends on the achievement of personal objectives, both qualitative and quantitative. Their determination and the evaluation of the results obtained form the object of a systematic annual interview.

Share in success

Sanofi-Synthélabo enables its employees to share in the group’s performance through:

- a profit-sharing scheme;
- a profit-sharing bonus, taking into account, besides the group’s overall performance, the performance of the employee’s operating unit;
- a company contribution complementing the employee’s payments into the group Savings Plan.

Introduced in the context of French legislation, these various measures apply to the 12,000 employees of the group working in France. One of the objectives of Sanofi-Synthélabo for 2002 is to implement, outside France, a group profit-sharing system, incorporating a bonus specifically based on the profits of each country.
Develop skills

Training must permit employees to develop existing skills or acquire new ones. It must also meet the general needs engendered by the growth and internationalization of the group. In 2001, Sanofi-Synthélabo privileged training in a certain number of priority areas identified: communication and staff management, mastery of new technologies, professional skills and support of employees faced with change. To reinforce the group’s cohesion around a common value system, management training is conducted at the group level.

Hours of training in 2001 by category

<table>
<thead>
<tr>
<th>Category</th>
<th>France</th>
<th>Other countries</th>
<th>World</th>
</tr>
</thead>
<tbody>
<tr>
<td>Managers</td>
<td>107,394</td>
<td>123,566</td>
<td>230,960</td>
</tr>
<tr>
<td>Sales force</td>
<td>50,037</td>
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<td>735,642</td>
</tr>
<tr>
<td>Other</td>
<td>167,919</td>
<td>191,624</td>
<td>241,661</td>
</tr>
<tr>
<td>Total</td>
<td>325,350</td>
<td>882,913</td>
<td>1,208,263</td>
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</table>

Favor professional growth

Annual development interviews, distinct from the evaluation interviews, permit each employee to express his or her professional plans for the future, in close cooperation with his or her direct manager. In Europe and North America, these interviews are now general practice. Their systematic use is being progressively extended to the rest of the world.

This dialogue promotes functional and geographic mobility, at the national or international level, organized through horizontal Careers Committees led by the Corporate Human Resources Department.

Welcome and maintain handicapped employees in the company

Sanofi-Synthélabo has a “Handicap Program”, the role of which is first, to allow handicapped employees to continue working through preventive measures and adaptation of work stations and organizations and second, to promote the insertion of handicapped persons in the company.

The way in which the issue of enabling handicapped employees to continue working is resolved determines the image of handicap within the company. By showing that it is possible to occupy a function, despite a handicap, without causing difficulties for fellow employees, encourages the overall welcome of handicapped employees.

Construct a social dialogue at the European level

An agreement was signed in December 2001 to create a European Industrial Relations Committee. A total of 20,690 employees are concerned. This Committee comprises 29 members from the 15 countries of the European Union. It anticipates the future expansion of the Union, with the presence of observers from those six countries which have a membership application currently under review: Cyprus, Estonia, Hungary, Poland, Czech Republic and Slovenia.

As a forum for information and dialogue, this Committee has the vocation of keeping abreast of the strategy of the group, the results achieved, the R&D policy, the evolution of industrial facilities and employment, as well as the life of the company in general. It will meet twice a year, or more often in the context of an exceptional event.

This agreement forms part of the group’s strategy, which aims to implement systems of employee representation and expression in all countries.
Sanofi-Synthélabo 54 Safety and environment

“Progress and commitment: our HSE policy”

In the service of life and health, Sanofi-Synthélabo adheres to an ambitious policy focused on protection of the safety of its employees and respect for the environment. It is expressed on a day-to-day basis by the experts working in risk identification and prevention, the annual progress objectives set for each site, the organization of a worldwide network of HSE coordinators to provide support to the line managers, and the regular appraisal of the results achieved, at the highest level of the group.

11.2 million euros dedicated to health, safety and environment in 2001.

40 % over three years: reduction in the accident frequency rate by millions of hours worked.

18 sites had “zero accidents” in 2001, one third of the total number of sites.
Mobilize scientific expertise to promote safety

The group’s 6,273 scientific and support staff help evaluate the impact of our products on human health. This expertise contributes to the implementation of the Health-Safety-Environnement (HSE) policy, from the stage of research and development of new compounds to drug manufacture, through two multidisciplinary committees:

• The COVALIS committee analyses all the chemical and pharmaceutical substances handled by the employees of the group and sets the levels of professional exposure appropriate for each of these. To date, 610 pharmaceutical active ingredients and 302 synthesis intermediates have been evaluated, comprising 90% of all substances used.

• The TRIBIO committee operates in the same way for biological agents, defining the rules of containment and individual or collective preventive measures to be respected.

All chemical processes are subjected to evaluation by the group’s Process Safety laboratory and Environmental laboratory.

The SAPHIR chemical synthesis workshops

• The growth of Plavix® and Aprovel®/Avapro® sales has led Sanofi-Synthélabo to construct chemical synthesis units for clopidogrel in Sisteron (France) and for irbesartan in Aramon (France). This overall investment of 250 million euros was crucial as regards both the capacity of the facilities (totaling 1,600 tons of powder handled per year) and the health and safety challenges. The risks faced by the personnel were both ergonomic and chemical in nature. The COVALIS committee had set the maximum limit of exposure at 50 µg/m³.

• The solutions adopted included the use of handling systems employing hermetically sealed containers and the installation of valves in the transfer system assuring product containment.

• These measures led to a substantially reduced need for individual protective equipment and for handling of drums, achieving a high level of safety while providing more comfortable working conditions.

Prevent risks in all our activities

Identify and evaluate the risks, develop preventive measures, monitor their efficacy, invest in training to integrate safety into professional practices: this rigorous approach is implemented worldwide to protect the health of our employees and preserve the environment of our sites.

Reducing the number and seriousness of work-related accidents implies looking at the potential risks from several angles simultaneously:

• The management of major industrial risks: studies on the hazards of industrial installations are complemented by hazard vetting procedures. Prior to any change in a product, process, installation or item of equipment, these permit assessment of the consequences of such a change, modification of the operating procedures or protective systems if appropriate, or organization of a training course. The hazard vetting approach is also being applied to existing processes. Dozens of processes have already been evaluated in various chemical and research units in France (Sisteron, Aramon, Porcheville, Montpellier), and the approach is currently being extended to all the group’s sites.

• The prevention of industrial accidents: internal inspections, crossover audits between sectors or units, “tracking down anomalies”, systematic analysis of the causes of any incident by a multidisciplinary team, etc. constitute an approach combining constant vigilance with implementation of a process of learning from experience that acts to drive progress.

• The safeguard of health at work: over and above the classical measures, Sanofi-Synthélabo has implemented new technologies of containment and hermetically sealed systems for powder transfer within its chemical and pharmaceutical units, eliminating manual handling and improving working conditions.

• The safety of medical sales representatives on the road.

The result of this preventive effort is measured by an index: the rate of accidents involving sick leave of more than 24 hours per million hours worked. This index showed a continuous decline from 1999 to 2001. The objective is to reach an overall rate of less than three by the end of 2002. In 2001, 18 sites achieved a “zero accident rate”, compared with nine the previous year.
Rate of industrial accidents

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<th>1999</th>
<th>2000</th>
<th>2001</th>
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<tbody>
<tr>
<td>Number of accidents</td>
<td>205</td>
<td>194</td>
<td>173</td>
</tr>
</tbody>
</table>

Careful driving by medical sales representatives

Young, newly recruited and eager to prove themselves: it is at this moment in their professional career that medical representatives sales are often most heedless of their own safety, while traveling thousands of kilometers by car annually for their job. The group’s 10,000 medical sales representatives account for a third of its total staff and Sanofi-Synthélabo has made their careful driving a priority objective. The pilot operation launched in France in 2000 was extended in 2001 to the Italian and German affiliates. Awareness and training initiatives are being conducted in liaison with team leaders, in conjunction with “careful driving” courses communicated via the internet or on CD-ROM in the U.S. and the U.K. The results are monitored centrally on the basis of special reports submitted by each unit of the group. These efforts led to a decrease of 23% in the rate of work accidents per 10,000 medical representatives during the year 2001.

Increase the accountability of our partnership network

Sanofi-Synthélabo includes its external partners in its rigorous approach to risk prevention. Whether suppliers, contractors or service companies, the safety factor is incorporated right from the invitations to tender and is one of the criteria for selection of outside partners. Toll manufacturers for chemical and pharmaceutical processes and companies transporting hazardous materials are specifically concerned. In the same spirit, a partnership agreement to ensure safety is signed with French companies providing temporary staff.

Respect the natural environment

Initiated in France and in developing countries, this policy has been progressively extended throughout the world. Increasing numbers of contacts and audits are being organized with the various suppliers, under the auspices of the group’s HSE coordinators and their local teams.

In 2001, the HSE Department conducted a survey of the group’s chemical suppliers, notably in India and China, to assess their performances in terms of hygiene and safety, as well as the extent of their concern for the environment. In conjunction with a quality audit, this approach is designed to help the group’s partners to identify possible shortcomings and to remedy them. The group takes care to implement all the technology transfers necessary, at the same time emphasizing its firm commitment to these values.

Water consumption (m³)

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<tr>
<th></th>
<th>1999</th>
<th>2000</th>
<th>2001</th>
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<tbody>
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<td>Chemical</td>
<td>2,982,515</td>
<td>3,287,269</td>
<td>3,654,583</td>
</tr>
<tr>
<td>Pharma.</td>
<td>2,367,233</td>
<td>2,116,613</td>
<td>2,460,026</td>
</tr>
<tr>
<td>Research</td>
<td>594,901</td>
<td>540,429</td>
<td>557,992</td>
</tr>
<tr>
<td>Distribution</td>
<td>15,773</td>
<td>20,928</td>
<td>20,928</td>
</tr>
<tr>
<td>Total</td>
<td>3,155,895</td>
<td>3,584,731</td>
<td>3,892,507</td>
</tr>
</tbody>
</table>

Water consumption: Between 1999 and 2001, water consumption relative to sales diminished by 7%.
Volatile organic components (VOC) (tonnes)

<table>
<thead>
<tr>
<th>Year</th>
<th>Chemical</th>
<th>Pharmaceutical</th>
<th>Research</th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>2,362</td>
<td>673</td>
<td>0</td>
<td>567</td>
</tr>
<tr>
<td>2000</td>
<td>2,508</td>
<td>596</td>
<td>10</td>
<td>522</td>
</tr>
<tr>
<td>2001</td>
<td>1,980</td>
<td>617</td>
<td>11</td>
<td>402</td>
</tr>
</tbody>
</table>

Air emissions: Between 1999 and 2001, the level of emissions relative to sales decreased by 29% for volatile organic components (VOC).

Hazardous waste* (tonnes)

<table>
<thead>
<tr>
<th>Year</th>
<th>Non utilized</th>
<th>Utilized</th>
<th>(g/k€) Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1999</td>
<td>18,040</td>
<td>26,000</td>
<td>8,232</td>
</tr>
<tr>
<td>2000</td>
<td>6,655</td>
<td>40,496</td>
<td>7,907</td>
</tr>
<tr>
<td>2001</td>
<td>1,489</td>
<td>49,152</td>
<td>7,805</td>
</tr>
</tbody>
</table>

Hazardous waste* European Union classification, May 3, 2000

Waste product utilization: Between 1999 and 2001, the production of hazardous waste relative to sales diminished by 5%. At the same time, the rate of utilization* of this waste increased from 59% to 97%.

Assessment of our action

The HSE policy is implemented by line managers through a yearly progress plan, the HSE Progress Action Plan (PASS). Compiled on a decentralized basis and adapted to each facility and unit, the PASS defines the objectives, plans of action and resources to be invested in each area according to the specific nature of the site. Adherence to the PASS is monitored monthly by the sector manager, quarterly by the site director and annually by the HSE Department. The results are communicated internally.

Assure transparency

Since its constitution in 1999, Sanofi-Synthélabo has compiled a consolidated report of its HSE policy, updates on program implementation and the results obtained. This information constitutes the basis of its internal and external communication, via intranet or internet, and provides a basis for its contacts with external partners on its various sites.

Ground cleanups, a key challenge

Sanofi-Synthélabo is concerned with the state of the ground and its cleanup, if necessary, at the end of its industrial use. In Brazil, the group is voluntarily participating in the cleanup of a supervised hazardous waste facility used during the 1980s by approximately 60 companies and managed at the time by a third-party company.